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USE OF THE VAGINAL SMEAR AS A SCREENING TEST*

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BOSTON

A LONG-RANGE experimental study, financed in part by the Commonwealth Fund, was inaugurated in January, 1945, by the Massachusetts Department of Public Health to evaluate, from an administrative standpoint, the use of vaginal smears in the diagnosis of uterine cancer. At that time the test was just beginning to be generally known and enthusiasm for its utilization was increasing.[1-5] Several lay periodicals were soon to advocate the universal examination of women by this test. The Department desired to determine whether the cytology test for cancer should be added to the other services offered to physicians and the public, whether the test should be made available to the cancer clinics either as a screening test for all female patients or as an additional diagnostic procedure for those with gynecologic conditions or whether the test should be ignored in the official cancer program.

This study was a joint project of the Massachusetts Department of Public Health, the Massachusetts Tumor Diagnosis Service, the State and the State-aided cancer clinics.

The plan of study was as follows: A single vaginal smear was to be obtained from each female who attended the cancer clinics between January 1, 1945, and June 30, 1947. Three years after the original smear a follow-up history and, whenever possible, a pelvic examination and a repeat smear were to be secured from these same patients. The details of the study can be found in the preliminary report published in 1948.[6]

Three forms of diagnostic terminology were used in this study: negative, positive and questionable. Biopsy and curettage were requested on persons with positive and questionable smears unless the smear had been confirmed by a biopsy, taken at the time of the smear.

Women showing carcinoma on the biopsy or curettings were not followed further for this study. For the remainder of the subjects in the study, the following procedure was utilized: At the expiration of three years from the date of the original smear the clinic records were consulted to determine whether or not the patient had died and, if so, the recorded cause of death. Letters were sent to those who were still living, requesting that they return to a clinic for a pelvic examination and a repeat smear. With the exception of a few who could not be located, those who failed to make such an appointment were visited and urged to come to a clinic. If they were unwilling to do so, a short history was taken of the medical problems of the subject during the three-year period since the first smear.

COMPARISON OF ORIGINAL SMEAR WITH REPEAT SMEAR

At the time of the three-year follow-up repeat smears were taken on 42.8 per cent of the series. Agreement between a single original smear and a repeat smear was present in 91.1 per cent of the subjects. The 8.9 per cent who showed disagreement between the two smears was subdivided as follows:

First smear questionable, repeat smear negative, 5.4 per cent
First smear negative, second smear questionable, 2.5 per cent
First smear negative, second smear positive, 0.3 per cent
First smear positive, second smear negative, 0.7 per cent

DETAIL OF ANALYSIS

The total number of records was 3581||; of this number 251 were discarded from the study because the subject had reported a previous hysterectomy. Some of this number would have had a cervical stump in which cancer might have developed; others could not have had cancer of the uterus due to the total extirpation of this organ. There were

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||The preliminary report[6] on the results of the original examination, made on February 9, 1948, was based on 3586 records but subsequent review has shown the true number to be 3581, omitting duplicates. The present data and that of the earlier study differ slightly, due to additional information now available and to changes in classification.

131 women with either a history or a present diagnosis of cancer of the bladder, ovary, rectum, ureter, urethra, vagina or vulva. Their records were discarded since there was a possibility that cells from these cancers might confuse the diagnosis.

There were 403 women who had a previous history of cancer of the uterus. Their records were omitted, since in some cases there was no accurate information concerning the activity of the cancer at the time of the smear, and other previous x-ray therapy might have altered the character of the cells. In addition to these, there were 159 who could not be traced and 142 whose smears were unsatisfactory: this left records of 2495 subjects, upon whom the study is based.

The records have been divided into three categories: Category I, women reporting no gynecologic symptoms; Category II, those with bleeding as a symptom; and Category III, those with other gynecologic symptoms.

Incidence of Cancer

The incidence of cancer of the uterus varies greatly in these different groups. It is low in the groups with no gynecologic symptoms, moderately high in the group with gynecologic symptoms other than bleeding and very high among women reporting bleeding as a symptom.

Classification by Smear Diagnosis

The records also have been divided into three groups according to the smear diagnosis: positive, negative and questionable. There were 154 positive smears, 180 questionable smears and 2161 negative smears.

The group whose smears were classified as questionable, in Table 2, is of particular interest. Although it was recognized that atypical cellular changes may be seen in benign as well as in malignant conditions, it seemed worth while to single out those cases in which the exfoliated cells were unusual without being definitely in the malignant category, in the hope that premalignant or early malignant changes might be identified. The main value of this group is, therefore, as material toward a study of premalignant and early malignant cellular changes. This should be a fruitful field for investigation and is one that has hardly been touched.[7]

One would expect cases of both advanced and early carcinoma in the group of "questionable" smears, and it was found that 27.8 per cent had cancer at the time of smear. One and one-tenth per cent developed cancer within three years. This figure corresponds with the incidence of carcinoma developing in the patients with bleeding, 1.4 per cent (Table 1), and is considerably higher than one would expect from a group of women without gynecologic symptoms or with symptoms other than bleeding. Sixty-two and two-tenths per cent of the questionable group had no apparent cancer at the time of smear or at the end of three years, and 8.9 per cent had no apparent cancer at the time of the smear but died within three years of other conditions.

Table 1. *Incidence of Cancer.*

	No. of Subjects	Percentage of Subjects With Cancer of Uterus		
		at time of smear	within 3 years	total
No gynecologic symptoms (Category I)	1654	0.5	0.3	0.8
Bleeding (Category II)	579	30.7	1.4	32.1
Gynecologic symptoms other than bleeding (Category III)	262	8.8	0.7	9.5
Total	2495			

Table 2. *Smear Diagnoses, Subdivided by Categories.*

	Uterine Cancer At Time of Smear (All Microscopically Proved)			No Apparent Uterine Cancer At Time of Smear or at End of 3-Year Period		
	classification A			classification B		
	Positive	Questionable	Negative	Positive	Questionable	Negative
Category I: Patients reporting no gynecologic symptoms	3 (*)	3 (4.7%)	3 (0.2%)	7 (*)	48 (75.0%)	1238 (78.5%)
Category II: Patients with bleeding as symptom	111 (90.2%)	42 (42.4%)	25 (7.0%)	11 (8.9%)	52 (52.5%)	308 (86.3%)
Category III: Patients with other gynecologic symptoms	17 (*)	5 (*)	1 (0.4%)	0 (*)	12 (*)	212 (93.4%)
Total number of patients with gynecologic symptoms	128 (90.8%)	47 (40.5%)	26 (4.4%)	11 (7.8%)	64 (55.2%)	520 (89.0%)
Total number of patients with and without gynecologic symptoms	131 (85.1%)	50 (27.8%)	29 (1.3%)	18 (11.7%)	112 (62.2%)	1758 (81.4%)

*Percentages only computed where total number of cases was greater than 50.

Of the positive smears (Table 2) 131 (85.1 per cent) were diagnosed as uterine cancer at the time of the smear; 18 (11.7 per cent) had no apparent uterine cancer at the time of the smear or at the end of the three-year period; 4 (2.6 per cent) had no apparent uterine cancer at the time of the smear but had cancer of the uterus within three years; and 1 (0.6 per cent) had no apparent uterine cancer at the time of smear but died within three years of a condition other than cancer of the uterus.

Of the 2161 with negative smears (Table 2), 1.3 per cent had uterine cancer at time of smear, 81.4 per cent had no cancer at time of smear or at the end of three years, 0.5 per cent developed cancer within three years and 16.8 per cent died of a condition other than cancer within three years.

Rates Based on Diagnoses

Although the more common practice has been to base the rates on smears rather than on actual diagnoses, it is believed that the latter method is better, and in the remainder of this paper it will be utilized.

Of the 210 women who were diagnosed as having cancer at the time of the original smear (Table 3), 62.4 per cent showed a positive test, 23.8 per cent a questionable test and 13.8 per cent a negative test. Thus, the tests failed to give any indication that cancer was present in nearly one seventh of those who had cancer of the uterus. Of the 1888 individuals who had no apparent cancer of the uterus at the time of the smear or three years later, 1.0 per cent originally showed a positive smear, 5.9 per cent a questionable smear and 93.1 per cent a negative one. The results were somewhat similar for those who died within the three-year period after the smear and were certified as dying of conditions other than cancer of the uterus (0.3, 4.2 and 95.5 per cent).

There were too few women who were found to have cancer of the uterus within the three-year period to warrant the computation of percentages. This classification, however, needs special comment. It is composed of sixteen subjects: 5 in Category I, 8 in Category II and 3 in Category III. These cases have been subdivided by the time interval between smear and diagnosis.

Ten of the 16 cases were diagnosed within the first year and 4 and 2 respectively in the next two years. Such a distribution probably indicates that several of the cancers were actually present at the time of the original smear. The number of cancer cases* that might be expected in each year was obtained. Thus, 1.8 cases were expected in the first year, compared with the 10 cases that were observed. In the second year, 1.6 cases were expected and 4 were observed; in the third year, 1.5 cases were expected and 2 were observed. The number of observed cases in the latter two years did not differ greatly from their expected values, but in the first year a significantly greater number of cases was observed than was expected.

According to the Poisson distribution,[8] the probability of observing by chance as many as 10 cancer cases when only 1.8 are expected would be 0.00003, which is extremely small. There is a possibility that the New York morbidity rates that were used might not be applicable to Massachusetts data or might be too low due to incomplete reporting in New York State. Although it is believed that the computed expected values are close to the true values, the possibility of error exists, but a 35 per cent increase in the expected values should lie well beyond such error. These values would be respectively 2.8, 2.5 and 2.3. With the expected number of cancer cases 2.8, the chance of obtaining as many as 10 cases would be .00083, which is still highly significant. Thus, it seems probable that 7 or 8 of

Table 2 (*Concluded*).

No Apparent Uterine Cancer at Time of Smear But Developed Within 3 Years — Classification C			No Apparent Uterine Cancer at Time of Smear; Patient Died Within 3 Years of Other Conditions — Classification D			Total		
Positive	Questionable	Negative	Positive	Questionable	Negative	Positive	Questionable	Negative
2 (*)	0	3 (0.2%)	1 (*)	13 (20.3%)	333 (21.1%)	13	64	1577
1 (0.8%)	2 (2.0%)	5 (1.4%)	0	3 (3.0%)	19 (5.3%)	123	99	357
1 (*)	0 (*)	2 (0.9%)	0 (*)	0 (*)	12 (5.3%)	18	17	227
2 (1.4%)	2 (1.7%)	7 (1.2%)	0	3 (2.6%)	31 (5.3%)	141	116	584
4 (2.6%)	2 (1.1%)	10 (0.5%)	1 (0.6%)	16 (8.9%)	364 (16.8%)	154 (100%)	180 (100%)	2161 (100%)

*Computation of expected value: Person-years were computed from the date of smear to the end of the first-year period in the case of the living and to the date of the death for the others. Utilizing the same methodology, person-years were computed from the end of the first year to the end of the second and from the end of the second to the end of the third. Expected values were computed by applying to the respective person-years age-sex specific-incidence rates furnished by the New York State Health Department. These rates were based on cancer reporting in New York State exclusive of New York City. The observed and expected values were as follows:

	First Year		Second Year		Third Year	
	Observed	Expected	Observed	Expected	Observed	Expected
Categories I-III..	10	1.8	4	1.6	2	1.5

the women developing cancer in the first year already had the disease at the time the smear was taken, that the 2 who developed cancer within the third year did not have it at the time of the smear, and that of the 4 who developed it within the second year, 2 or possibly 3 could have been free from the disease at the time of the smear.

Table 4 shows the classification for women who reported no gynecologic conditions.

Table 5 shows the classification for the women who reported bleeding as a symptom. Of those who had cancer, 62.4 per cent had a positive smear, 23.6 per cent a questionable smear and 14.0 per cent a negative one. Among those who were free from cancer at the end of the three-year period 3.0 per cent had positive smears, 14.0 per cent questionable smears and 83.0 per cent negative ones.

Table 6 shows the classifications of women who came to a clinic with gynecologic symptoms other than bleeding. The one classification for which percentages could be obtained (B) was reasonably consistent with comparable data in the nongynecologic categories but not with the data of the group reporting bleeding.

TABLE 3. *Results of Cytology Test in Combined Categories I–III.*

	Smear Diagnosis				Percentage Based on Diagnosis			
	POSITIVE	QUESTIONABLE	NEGATIVE	TOTAL	POSITIVE	QUESTIONABLE	NEGATIVE	TOTAL
Classification A: Uterine cancer when smear taken..	131 (181)	50	29	210	62.4 (86.2)	23.8	13.8	100.0
Classification B: No apparent uterine cancer when smear taken or at end of three-year period	18 (130)	112	1758	1888	1.0 (6.9)	5.9	93.1	100.0
Classification C: No apparent uterine cancer when smear taken but developed within three years ..	4 (6)	2	10	16	*		*	
Classification D: No apparent uterine cancer when smear taken but patient died within three years, of other condition	1 (17)	16	364	381	0.3 (4.5)	4.2	95.5	100.0
Totals	154 (334)	180	2161	2495	6.2 (13.4)	7.2	86.6	100.0

*Rates not computed, as cases too few in number.

Cost of the Smear

In this study, as well as in others, a few unsuspected cases of cancer have been discovered through the use of the vaginal smear, but their numbers appear small in relation to the amount expended. The cost for collection and examination was slightly over $3.00 per specimen. The group of 1654 women with no gynecologic symptoms produced 9 cancers, 3 of which were discovered by the smear. Thus, the cost per discovered case was approximately $1700.

Moreover, if this service were given to all adult females in Massachusetts as a routine screening procedure, the cost would be greater than the combined budget for all other cancer services now provided by the State.

In view of the circumstances, it seems impractical to consider the use of the vaginal smear as a routine screening procedure.

TABLE 4. *Category I: Subjects With No Gynecologic Symptoms.*

	Smear Diagnosis				Percentage Based on Diagnosis			
	POSITIVE	QUESTIONABLE	NEGATIVE	TOTAL	POSITIVE	QUESTIONABLE	NEGATIVE	TOTAL
Classification A: Uterine cancer when smear taken..	3 (6)	3	3	9	*	*	*	
Classification B: No apparent uterine cancer when smear taken or at end of three-year period	7 (55)	48	1238	1293	0.5 (4.2)	3.7	95.7	99.9
Classification C: No apparent uterine cancer when smear taken but developed within three years ..	2 (2)	0	3	5	*	*	*	
Classification D: No apparent uterine cancer when smear taken, but patient died within three years, of other condition	1 (14)	13	333	347	0.3 (4.0)	3.7	96.0	100.0
Totals	13 (77)	64	1577	1654	0.8 (4.7)	3.9	95.3	100.0

*Rates not computed, as cases too few in number.

Discussion

Although a number of reports on the large-scale use of the vaginal smear have appeared, there is still no settled opinion about its value in screening. Most of these reports have dealt with the use of the

vaginal smear in discovering early carcinoma and carcinoma *in situ*, focusing on the pathologic and clinical aspects of the problem.[9-16] It is believed that no other study to determine the value of a single vaginal-smear examination as a public-health measure has been published. The requirements for the successful use of this technic for screening purposes are obviously different from those that would be satisfactory in the study of persons with obscure or borderline disease, since both the percentage of erroneous diagnoses based on single smear examinations and the cost of the procedure on a large scale must be considered.

It is desirable to arrive at some estimate of the accuracy of the test. Obviously, the 29 (14 per cent) negative smear diagnoses among the 210 persons with uterine cancer at the time of the smear were erroneous (Table 3), as well as the 18 positive diagnoses out of 1888 (1 per cent) with no apparent uterine cancer at the end of the three-year period. The smears of the women who died within three years of conditions other than cancer of the uterus may or may not have been erroneously diagnosed.

Among the 16 women who developed cancer within the three years, there is a probability of several erroneous diagnoses. Therefore, there were definitely 47 and probably a few more erroneous diagnoses.

Erroneous diagnoses are the results of faulty interpretation, resulting from inexperience or inaccurate observation, or a deficiency in the specimen that is not representative of the condition present.[5, 10, 17] This is well illustrated in an analysis of the 47 apparently definite errors in diagnosis. These were reviewed by two experienced workers without knowledge of the original diagnoses or the clinical findings. Both reached the same conclusions independently. Thirteen mistakes in diagnosing the first smears were rectified on re-examination of the slides; 6 were considered inconclusive and were classified as questionable on re-examination; 28 smear diagnoses could not be reconciled with the clinical findings. Twenty-two of these represent smears that on re-examination were still considered nonmalignant although the clinical diagnosis was cancer, and 6 were smears that were still considered positive despite the clinical diagnosis of no cancer.

TABLE 5. *Category II: Patients With Bleeding as a Symptom.*

	Smear Diagnosis				Percentage Based on Diagnosis			
	POSITIVE	QUESTIONABLE	NEGATIVE	TOTAL	POSITIVE	QUESTIONABLE	NEGATIVE	TOTAL
Classification A: Uterine cancer when smear taken	111	42 (153)	25	178	62.4	23.6 (86.0)	14.0	100.0
Classification B: No apparent uterine cancer when smear taken or at end of three-year-period	11	52 (63)	308	371	3.0	14.0 (17.0)	83.0	100.0
Classification C: No apparent uterine cancer when smear taken but developed within three years	1	2 (3)	5	8	*	*	*	
Classification D: No apparent uterine cancer when smear taken, but patient died within three years, of other condition	0	3 (3)	19	22	*	*	*	
Totals	123	99 (222)	357	579	21.2	17.1 (38.3)	61.7	100.0

*Rates not computed, as cases too few in number.

TABLE 6. *Category III: Subjects With Other Gynecologic Symptoms When First Smear Taken.*

	Smear Diagnosis				Percentage Based on Diagnosis			
	POSITIVE	QUESTIONABLE	NEGATIVE	TOTAL	POSITIVE	QUESTIONABLE	NEGATIVE	TOTAL
Classification A: Uterine cancer when smear taken	17	5 (22)	1	23	*	*	*	
Classification B: No apparent uterine cancer when smear taken or at end of three-year period	0	12 (12)	212	224	0.0	5.4 (5.4)	94.6	100.0
Classification C: No apparent uterine cancer when smear taken but developed within three years	1	0 (1)	2	3	*	*	*	
Classification D: No apparent uterine cancer when smear taken, but patient died within three years, of other condition	0	0 (0)	12	12	*	*	*	
Totals	18	17 (35)	227	262	6.9	6.5 (13.4)	86.6	100.0

*Rates not computed, as cases too few in number.

There is a possibility that some of this latter group might eventually be diagnosed as carcinoma *in situ*, and the need for a long-range study is apparent. These 6 cases will be followed until sufficient time has elapsed to rule out any possibility of malignancy.

Among the group with questionable smears, neither false positive nor false negative diagnoses can be recorded. If these were eliminated, the incidence of erroneous diagnoses among the 2315 remaining subjects would be at least 2.0 per cent; however, if these records were divided into those women who reported bleeding and those who did not, the percentage of erroneous diagnoses would be 7.5 per cent among the bleeders and 0.6 per cent among the others.

From an administrative point of view, the smears diagnosed as questionable should be combined with those diagnosed as positive, inasmuch as there must be further study of the subjects in both these groups. The rates in italics in Tables 4 and 5 have been obtained by combining the positive and the questionable groups. As a result, the percentage of erroneous diagnoses would be 13.8 for cancer cases and 6.9 for non-cancer cases (Table 3). Among the bleeders the respective rates would be 14.0 per cent for cancer cases and 17.0 per cent for non-cancer cases. The over-all error in the present study was about 7.0 per cent when these two groups were combined, contrasted with about 2.0 per cent when the questionable group was omitted.

Summary

A study was made of the value of a single vaginal smear as a diagnostic procedure in cancer of the uterus. The incidence of cancer among women without gynecologic symptoms was less than 1 per cent, and among those with other gynecologic symptoms it was about 10 per cent. If questionable smears were considered positive, the over-all error among symptomless subjects would be at least 4 per cent and among those with bleeding at least 16 per cent. If the questionable smears were omitted, erroneous diagnoses would be less than 1 per cent among symptomless women and nearly 8 per cent among those reporting bleeding. The percentage of questionable diagnoses was about four times as great among those with bleeding as among those who did not mention bleeding. The large error found among the group most likely to have cancer, — the bleeders, — impairs the value of this test as a diagnostic entity for screening purposes. It does not seem feasible for a state health department to offer this test on an extensive scale for women without gynecologic symptoms, as the cost would be prohibitive and the number of cancers found would be relatively few.

It should be reiterated that in this discussion we are not concerned with the value of the vaginal smear as a means of diagnosis *per se* but rather with its use as a method of screening large populations. Cytologic diagnosis as an adjunct to biopsy, particularly in the study of obscure and borderline lesions, is an entirely different problem from that broached in this investigation. The value of this technic as a screening procedure is obviously limited as compared to its usefulness in the study of a given case.

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DEEP VENOUS THROMBOSIS IN THE LEG FOLLOWING EFFORT OR STRAIN*

CHILTON CRANE, M.D.†

BOSTON

SO-CALLED "effort thrombosis" of the axillary or subclavian vein has been the subject of at least 70 communications in the literature since 1930; upwards of 300 cases have been reported.[1-8] Deep venous thrombosis of the lower extremity secondary to fracture, joint injury or external trauma represents an all too familiar entity. Indeed, Vance[9] was able to report a series of 34 autopsied cases of fatal pulmonary embolism following fractures of the lower extremity, and Martland[10] reported 55 autopsied cases of fatal pulmonary embolism following various leg injuries. Bauer[11] has pointed out that venous thrombosis is 12 times more common in cases of leg injury than in any other group of cases. In contrast to these well recognized categories, deep venous thrombosis involving the legs, brought on by effort or strain, without external trauma or joint or bone injury, has received very little attention. In 1938 Homans,[12] in describing venous thrombosis in the calf muscles, stated that "a very extensive process causes swelling and perhaps cyanosis of the ankle, or even of the calf. But as a rule the disease is very silent. The exciting cause is usually some minor injury or strain of the lower leg or foot." In 1941 Kaplan[13] reported 3 cases of deep venous thrombosis in the leg following uncomplicated effort or strain; he pointed out that this symptom complex constituted a distinct entity. The purpose of this report is to present brief histories of 13 cases of this syndrome, to tabulate the essential features of 10 cases garnered from the literature, to speculate briefly on the etiologic mechanism of this type of venous thrombosis and to suggest criteria for the diagnosis.

It is of interest that symptoms in the first 4 of such cases to be described occurred after a "step-up test" that has been used for many years in the Department of Hygiene at Harvard University as a physiologic screening test for all freshman students. In the course of this test the student steps up onto and then down from an 18-inch platform once every four seconds for five minutes in response to the directions of a phonograph record. He may use either leg or may change from right to left as he sees fit. This "step-up" test in relation to venous thrombosis seems to offer an ideal example of a semi-controlled effort or strain.

CASE REPORTS

CASE 1. C. M., a 19-year-old college student, entered the Peter Bent Brigham Hospital 5 days after taking the "step-up test." He had noted no discomfort during the test or during the ensuing 48 hours, but at the end of the 2nd day a dull ache appeared in the right calf. This persisted and became associated with a feeling of heaviness and lameness in the right lower leg. Physical examination 3 days later showed tenderness of the upper third of the right calf, with measurable enlargement of the right calf as compared with the left. There was edema of the lower leg and ankle. The superficial veins were not unduly prominent. Two firm cord-like structures were palpable deep in the calf muscle; these were thought to represent thrombosed veins. There was marked pain on dorsiflexion of the foot. The arterial circulation was normal; there was no ecchymosis at any point, and none appeared subsequently.

The patient was treated with strict bed rest, elevation of the legs, compression bandages and heparin for 7 days, with complete relief of symptoms and complete subsidence of all swelling and tenderness.

Twenty-five months later, this student continues to note some heaviness and lameness in the right leg after prolonged walking or standing, and the superficial veins are more prominent than those of the left leg.

CASE 2. A. W., a 21-year-old college student, entered Stillman Infirmary of Harvard University 3 days after taking the "step-up test," in which he used both legs equally. He had noted no discomfort or disability during or after this test until 48 hours later, when he began to suffer from stiffness and soreness in the left calf that were made worse by long standing. Simultaneously, he developed a slight limp. Examination revealed tenderness in the popliteal space and induration in the region of the popliteal vessels. The left calf was diffusely tender to direct palpation and to lateral compression and was definitely firmer than the right calf. Homans' sign was markedly positive. There was no swelling or detectable color change in the limb. The arterial circulation was normal.

This patient was treated, under a preliminary diagnosis of muscle strain of the left calf, by bed rest, elevation and compression bandaging of the leg and large hot moist packs on the affected leg. Three days later the subjective pain in the calf and behind the left knee had disappeared; only slight tenderness remained in the calf muscle and along the course of the popliteal vein. After 3 more days he gradually became ambulant, without return of signs or symptoms. There was no evident ecchymosis. No follow-up data are available in this case.

CASE 3. F. W. G., a 24-year-old college student, entered the Stillman Infirmary 4 days after carrying out the "step-up test." On the day following this test he felt some soreness in the right calf. Two days later the right calf seemed to him larger than the left, even though the soreness was diminishing. On the 4th day the right ankle became swollen for the first time; because of this swelling he came to the infirmary. Examination on admission showed slight pitting edema of the right ankle and lower leg to the level of the tibial tubercle. There was diffuse tenderness in the calf and pain on passive dorsiflexion of the foot. There were no superficial thrombosed veins; no tenderness was noted in the thigh. No note was made of any color change in the limb or concerning the prominence of the superficial veins.

This student was also assumed at the outset to have a calf-muscle strain and was treated with bed rest, hot packs and elevation of the leg. Three days later all signs and symptoms had vanished, and the patient was discharged on the 6th hospital day.

In response to a follow-up letter sent 5 years later, this patient states that he considers his left leg entirely normal.

CASE 4. A. C. F., a 19-year-old college freshman, entered Stillman Infirmary 1 week after taking the "step-up test." He also had noted no symptoms until 2 days later, when the left calf became sore. Four days after the test he began to limp and observed an increasing tenderness and disability

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of the left lower leg. Examination on admission showed the left calf to be diffusely tender, diffusely swollen and indurated. The dorsiflexion sign was markedly positive. There was no ecchymosis. The surface veins in the left leg did not seem unduly prominent, nor was there any detectable alteration in the color of the limb. The arterial circulation was normal.

The patient was treated with bed rest, elevation and hot packs, with a diagnosis of gastrocnemius strain. Two days later all signs and symptoms had disappeared; he was discharged on the 4th hospital day. Eighteen months later the left leg was entirely normal.

[Significant is the fact that 2 of these 4 remarkably similar cases were referred by a surgeon thoroughly familiar with athletic injuries, who appreciated that the most telling symptoms and signs were not those of muscle injury.]

CASE 5. R. G., a 55-year-old college professor, had been playing handball for about 15 minutes when he noted what he described as a sudden "cramp" in the right calf. The calf became increasingly stiff and painful, and he was forced to discontinue playing 2 or 3 minutes later. When seen on the following afternoon, he was limping and complaining of stiffness and aching pain in the right calf. The circumference of the right calf was 1 cm. greater than that of the left. There was diffuse swelling and induration throughout the calf muscle, and considerable tenderness was present over the vascular trunks in the popliteal space. The dorsiflexion sign was markedly positive. The arterial circulation was normal; no change in color or temperature of the right leg could be made out. The patient was treated with strict bed rest, elevation of the foot of the bed and compression bandages. Two days later there was less pain and less tenderness, but the measurable enlargement of the right calf had increased by 1 cm. After another 4 days in bed all signs and symptoms disappeared and the patient was gradually mobilized. Thirty months later the patient considered his right leg entirely normal.

CASE 6. J. W. G., a 53-year-old executive, had been kneeling down for 2 or 3 minutes while changing an automobile tire; on rising to a standing position he noted a sudden, fairly severe pain in the right popliteal space. This pain disappeared in a few minutes' time, but on that evening he noted some soreness in the right calf; the calf became more stiff and painful on the following day. By the evening of the day after the onset, some swelling of the right ankle and calf was present. He began to limp because of stiffness and soreness, and each evening the swelling of the lower leg and ankle reappeared. When he was seen 10 days later the diameter of the right calf was ½ inch greater than the left. Tenderness and induration were diffusely present in the calf muscle; these signs extended into the popliteal space. There was no ecchymosis and no evident change in skin color, and the arterial circulation was normal.

Strict bed rest with elevation of the legs was strongly urged on the patient but was only partially carried out. Compression bandages were applied and an elastic stocking ordered. Five days later the swelling had disappeared, but some tenderness and induration remained in the calf muscle. There was tenderness over the medial head of the gastrocnemius muscle. An additional 4 days of bed rest was advised, but the patient continued to work intermittently. Two months later he was still having intermittent evening swelling of the right ankle, but no other signs or symptoms were noted.

CASE 7. T. J. C., a 65-year-old executive, while riding horseback (using an English saddle) noted discomfort and stiffness in the left calf; he continued riding daily for several days, however, with some improvement in these symptoms. The leg continued to trouble him to a mild degree for the next 2 weeks. At the end of this time the stiffness increased, he began to limp and he noted a steady aching pain in the left calf at night. The left calf began to swell.

When he was seen 2 weeks after onset, the diameter of the left calf was 3/4 inch greater than the right; there was considerable tenderness and induration along the course of the posterior tibial vein and to a lesser degree over the gastrocnemius muscle. The medial muscle belly of the left gastrocnemius was slightly bulging and asymmetrical as compared with that on the right. After 2 days of bed rest and elevation the leg was much improved symptomatically. Only 1/4 inch of swelling remained, and there was less firmness and tenderness in the calf muscle. Two weeks later the circumference of the left calf was 1/4 inch less than the right. All tenderness and induration had vanished, but the superficial veins were definitely more prominent than previously. The patient was advised to wear an elastic stocking. Four months later the patient's only complaint was an "occasional catch in the top of the left calf when walking upstairs."

[For the data on Cases 8 to 13 the author is indebted to Dr. John Homans.]

CASE 8. R. P., a 58-year-old wool dealer, jumped up onto a bale of wool and felt something "give way" in his left leg. The following morning he found himself very lame; within 48 hours considerable swelling was present in the left calf, and he was limping from pain and stiffness in the leg. He was treated initially by his own physician, with a diagnosis of muscle strain in the left calf. As the swelling persisted, the diagnosis was changed to venous thrombosis. Examination on the 9th day of his disability showed a very lame left leg, considerably swollen below the knee, the calf being decidedly tense but showing no blueness and very little edema at the ankle. There was no ecchymosis, and the arterial circulation was normal. The diameter of the left calf was 2 cm. greater than that of the right. There was tenderness to deep pressure over the calf and along the course of the deeper veins up to the midcalf region. There was pain on dorsiflexion of the foot. The patient was treated with strict bed rest, elevation of the foot of the bed, heparin and dicumarol. He made an excellent recovery.

CASE 9. R. W. C., a 48-year-old businessman, was playing tennis when he landed rather sharply on his left foot. There was immediate acute pain in the left calf, followed by tenderness, swelling and ecchymosis. He continued playing tennis for the next several days until prevented by swelling and pain in the left lower leg. After this, three episodes of bed rest temporarily relieved the pain and swelling, but shortly after getting up each time swelling, limping and stiffness would supervene. Physical examination 40 days later showed edema of the left foot and ankle and mild cyanosis. The left foot was colder than the right, and the dorsalis-pedis pulsations were weaker in the left foot. On this day a superficial femoral-vein division was performed, together with a local periarterial stripping. Immediately after operation the foot became pink and warm, and all signs rapidly disappeared. One month later the left leg was entirely normal; 10 years later the patient states that it is still normal.

CASE 10. J. M. H., a 27-year-old lawyer, while playing golf twice jumped across a ditch on the golf course. On the next morning he noted a slight feeling of tension or soreness in the upper part of the left calf. Two days later there was considerable swelling of the left calf and ankle. By the 4th day he had marked discomfort in the calf, and the swelling had increased. Examination at that time showed the left ankle to be 1 inch larger than the right and the midcalf to be 2½ inches larger than the right. Examination of the thigh showed no tenderness and no thickening in Scarpa's triangle. The left dorsalis-pedis pulsation was questionably present. Gentle dorsiflexion of the foot caused a disagreeable sensation in the calf.

The patient was treated with strict bed rest, with elevation of the foot of the bed. Two days later the left-calf measurement had decreased by 1¼ inches. After 10 days of strict bed rest and exercises in elevation the patient gradually resumed his normal activities. One month after onset both legs measured exactly the same and the patient was symptom free. A follow-up letter 10 years later indicated that the left leg had been and was entirely normal.

CASE 11. C. H. S., a 34-year-old lawyer, stamped his right foot heavily on the starting crank of a motorcycle. This motion was repeated vigorously about 25 times. There was slight bruising of the posterior calf on a metal crossbar, but this did not become painful or bothersome. On the following day there was some lameness and a sense of heaviness in the right leg, followed 2 days later by swelling and increased pain in the right calf. The right calf continued to be painful and swollen; examination 4 weeks after onset showed a positive dorsiflexion sign, distinct cyanosis of the right foot on standing and increased firmness throughout the right calf. The right leg was larger than the left.

The patient was hospitalized and was treated with elevation and bandaging of the legs. Two months later the leg was

normal. There has since been a recurrence of thrombosis in this leg after skiing.

CASE 12. H. E. A., a 56-year-old businessman, while running to catch a train felt a sudden sharp pain in the right posterior midcalf that made him feel as if he had been kicked. Soreness in this calf persisted on walking, and 3 days after onset, on stooping, he felt another snap in the right calf, after which swelling appeared over the ankle and lower leg. Examination 9 days after onset revealed ++ pitting edema of the right leg extending up to within 5 cm. of the tibial tuberosity. There was definite calf tenderness and a positive dorsiflexion sign. There were irregular areas of ecchymosis on the anterior surface of the right ankle. There was faint cyanosis of the ankle on standing.

The patient was hospitalized for 12 days and was placed on a regimen of strict bed rest, elevation of the legs and dicumarol. At the time of discharge all signs and symptoms had disappeared.

CASE 13. J. B. H., a 70-year-old woman, started to walk upstairs, when her weighted foot slipped off the edge of a step and came down sharply on the step below. On the next day she noticed slight lameness in the back of the calf; that night she noted the sudden onset of pleuritic pain in the chest. Examination on the following day showed tenseness and tenderness in the calf, with a positive dorsiflexion sign. There was cyanosis about the ankle but very little edema. A chest film demonstrated the presence of a pulmonary infarct. Treatment, consisting of strict bed rest and 12 days of dicumarol therapy, resulted in complete abatement of all signs and symptoms.

Table 1 lists 10 cases of deep venous thrombosis in the leg following uncomplicated effort or strain, as reported in the literature since 1930.

PROBABLE ETIOLOGIC MECHANISMS

In the causation of this type of venous thrombosis it is certain that at least two of the following factors, acting in conjunction, play a chief role:

Markedly Increased Pressure in the Femoropopliteal Veins

Mengert and Murphy[18] have recorded intra-abdominal pressures as high as 200 mm. of mercury when patients strain voluntarily. These high intra-abdominal pressures, which accompany fixation of the diaphragm and contraction of the abdominal musculature, as in straining, lifting, and jumping, must be directly reflected by sharp venous pressure elevations in the vena cava, iliac veins and then the femoropopliteal veins, in accordance with Pascal's law, which states that pressure applied to an enclosed fluid is transmitted equally in all directions and acts with equal force on equal surfaces. Adams[19] recorded venous pressures in the foot as high as 224 mm. of mercury in patients with varicose veins after straining in the upright position. The venous wall (from the inguinal ligament down), the recipient of these high pressures, must vary markedly from place to place in the firmness of its muscular and fascial support. Any local weak point, such as the foramen ovale, would permit a bursting force to be applied to the vein wall or to a venous valve situated there. The importance of valvular disease is suggested by the finding of McLachlin and Paterson[20] in their recent excellent autopsy study that 23 of 76 venous thrombi had their origin in valve pockets.

Muscular Contraction in the Limb

This may be sudden and violent or moderate but repeated. In most situations of effort (jumping, landing after a fall or after a jump, lifting) the large flat muscles of the calf and the quadriceps group of the thigh contract simultaneously. This means that the great veins of the calf are compressed sharply against the posterior tibial wall, thus pumping venous blood forcibly through the relaxed muscular compartment surrounding Hunter's canal. If the pressure in the femoropopliteal vein is already very high, an additional bursting force is created.

Violent or repeated muscular contraction, when added to the high venous pressure factor, may also contuse the thin-walled vein, bruise the vasa vasorum or, in association with a muscle tear, rupture a venous branch at its point of origin, thus tearing a hole in the wall of the main venous trunk.

Peripheral Venous Engorgement

This may be caused by extreme anatomic venous angulation in the popliteal space, as in kneeling or squatting. It may also be caused by tendinous pressure on the popliteal vein. McLachlin and Pater-

TABLE 1. *Reported Cases of Deep Venous Thrombosis in the Leg Following Effort or Strain.*

AUTHOR	PATIENT	AGE	EFFORT	EVIDENCE OF THROMBOSIS	SITE OF THROMBOSIS
Kaplan[18]	Truckman	26	Lifting 200-lb. carton	Edema of entire left leg	Iliac vein
	Paper cutter	28	Slipped on roll of paper, twisting left knee.	Edema of left calf	Popliteal vein
	Painter	47	Twisting fall (4 ft.) off scaffolding onto feet	Edema of left leg, later of right leg	Iliac vein; ? vena cava
Laubie[14]	Farmer	57	Misstep while mounting a horse	Tenderness over femoral vein, edema of calf and ankle	Femoral vein
Leonelli[15]	Iron worker	70	Stumbled on step — slight twist of foot	Edema of left leg and thigh	Iliac vein
Cottalorda[16]	Man	24	Fell — slight twist of left knee; no direct trauma	Edema of calf, ankle and thigh	Femoral vein (at operation)
Rixford[8]	Man	55	Fall (7 ft.) onto feet, doubling up legs.	Edema of entire left leg, later of right leg	Iliac veins ? vena cava
	Man	54	Helping fellow worker lift 195-lb. veal onto hook	Edema of right ankle and calf, later of thigh	Popliteal vein, to femoral, to iliac
Garcelon[8]	Woman	55	Setting-up exercises	Edema of entire right leg	Femoroiliac veins
McCutchen and Cantey[17]	Man	62	Squatting	Edema of entire left leg	Iliac vein (at operation)

son state that "the fibrous band of origin of the soleus muscle appears to be a distinct constricting force on the vessels returning from the calf." Thus, if venous blood under pressure is trapped in the calf, sudden added contraction of the calf muscles may again cause rupture of a vein wall or valve.

However it is caused, the primary lesion in this type of venous thrombosis seems to be an injury to the wall of a main venous trunk concerned (perhaps often at a valve-wall junction), with thrombus formation in the classic pattern following at the site of injury. The evidence for this is seen in several directions: Delarue[21] found clear microscopical proof of complete rupture of the wall of the resected axillary vein in a fresh case of effort thrombosis involving the arm. The immediate severe pain radiating along the main vascular trunks as seen in Cases 1 and 2 in Table 1 suggests hemorrhage into the surrounding vascular sheath.

The rare occurrence of deep venous thrombosis after forcible rupture of many communicating veins during the widely practiced operation of greater-saphenous-vein stripping suggests that injury to venous branches at a distance from the main trunks is harmless. The fact that this syndrome is seen unilaterally and in healthy, apparently normal persons obviously tends to rule out an abnormality of the blood-clotting mechanism.

The key to the diagnosis of this disease is seen in the separation of the symptoms and signs of a muscle strain from those of a deep venous thrombosis: the stiffness, pain, and disability of a muscle strain are due to hematoma formation, and thus usually approach their height in four to twenty-four hours; the stiffness, pain and disability of a venous thrombosis follow the gradual establishment of a sufficient degree of venous blockade, which usually requires from two to seven days. The edema (if any) associated with a muscle strain appears in a matter of a few hours and is local; the edema of venous thrombosis does not appear for two to seven days and is diffuse. The tenderness and induration of a muscle strain are limited to the point of muscle tear and the area of hematoma formation; the tenderness and induration of a venous thrombosis will follow the course of the vascular trunks or may approach the area of swelling in diffuseness. Moderate to marked muscle rupture often leads to the gradual appearance of ecchymosis; venous thrombosis of itself never causes ecchymosis.

Homans' sign will, of course, almost always be positive in cases of calf-muscle strain. Dilatation of the superficial veins and a bluish tint to the leg help to confirm the diagnosis of venous thrombosis.

It is plain that muscle strain and venous thrombosis will often coexist in these cases. A study of the case histories above, however, makes one believe that the strain factor is a relatively minor one.

Discussion

This disease occurs prevailingly in men; at least, it is rarely recognized in women. It is generally unilateral at the outset. Pulmonary embolism is rare and in younger patients is virtually unknown. Strict bed rest, with elevation and compression bandaging of the legs and leg exercises, until all signs and symptoms have subsided, constitutes the best therapeutic regimen. The efficacy of such therapy in venous thrombosis of ambulatory life when confined to the lower leg was pointed out by Homans,[22] who also stated that recurrence often followed return to full activity. In view of this likelihood of recurrence and in order to obviate the remote possibility of pulmonary embolism, the addition of anticoagulants is desirable. Femoral-vein division should not be considered unless pulmonary embolism has supervened or unless signs and symptoms persist after six to eight weeks of conservative therapy.

It is probable that venous thrombosis in the lower extremity following effort is fairly common and that effort or strain may in reality be the initiating factor in a significant proportion of cases of so-called "idiopathic" or "walking phlebitis," particularly if fairly minor degrees of "effort" are considered. If venous thrombosis can be caused by an "infraction" principle, as in the "step-test" cases or in running for a train, may this mechanism not apply to the fat man climbing to his fourth-floor apartment? If working in, and then rising from, a position of kneeling or squatting can produce venous thrombosis, may not this common act be causative in some of the many outpatients who display the postphlebitic syndrome but no history of phlebitis? If lifting and jumping can cause venous thrombosis, how many "muscle strains" have been followed by chronic edema and induration?

Any patient suffering from a calf-muscle strain should be closely observed for the first ten days for evidence of venous thrombosis. Any otherwise well and active person who presents himself with signs of venous thrombosis in the leg should be carefully questioned for a history of antecedent effort or strain.

Summary and Conclusions

Brief histories of 13 cases of deep venous thrombosis in the leg following effort or strain are presented.

Essential features of 10 similar cases collected from the literature are tabulated.

Probable etiologic mechanisms underlying this syndrome are discussed.

The differential diagnosis of muscle strain is outlined.

The suggestion is made that effort or strain is the chief causative factor in many cases of venous thrombosis in the lower extremity occurring in active, healthy persons.

Addendum

Since this paper was submitted for publication, 3 additional cases have been observed.

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ALLERGY TO VIRAL AND RICKETTSIAL VACCINES*

III. Influence of Repeated Inoculations on the Acquisition of Egg Allergy

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THE problem of the possible acquisition of hypersensitivity to egg protein from repeated injection of vaccine derived from viruses or rickettsiae and propagated on chick embryo is a subject of current interest. An editorial comment[1] on an article published by us[2] raised this question and maintained that it is a possibility that must be seriously entertained, as follows: "The immunity following the injection of influenza vaccines is short-lived, and reinjections at least every two or three years and perhaps again at the first evidence of an outbreak seem to be the only long range method of effective control with the vaccines now available. The danger of such frequent reinjections must be weighed against possible benefits." We have put the thesis to the test in normal and allergic children to determine whether repeated injections would provide sufficient allergic stimulus to result in the acquisition or enhancement of egg allergy and are reporting our findings herewith.

Repeated Injections of Influenza Viral and Mumps Vaccine in Nonallergic Children

A total of 319 children (Table 1) under treatment for tuberculosis in the Children's Division of Sea View Hospital were injected with chick-egg-propagated influenza viral vaccine or mumps viral vaccine or both. Prior to the immunization procedure, the children were tested intradermally for sensitivity to egg proteins and vaccines. After the immunizing injections, additional tests were made to ascertain whether sensitivity had been acquired. Aside from the egg-chicken protein tests, 86 of these subjects were injected with influenza and mumps vaccines, 77 received influenza vaccine alone, and 124 received mumps vaccine. Thirty-two children served as a control group; in them only the egg-chicken protein tests were made. The injections were given at varying intervals over a period ranging from twelve to twenty-seven months; the total number of injections per subject ranged from 11 to 35.

Five in 319, or 1.6 per cent, of these subjects developed a dermal sensitivity to egg white.

Analysis of the Five Cases That Developed Skin Sensitivity

Two children with no previous sensitivity to egg protein developed a dermal reaction to egg white eight weeks after 2 intradermal prophylactic doses (0.1 cc.) of influenza vaccine. This reactivity was not further enhanced by two additional subcutaneous inoculations of larger doses (1.0 cc.) of vaccine given three months later. Additional subcutaneous injections of mumps vaccine, given nine months later, likewise failed to enhance the skin response. During the entire period of observation (twenty-seven months), these two patients had a total of 35 experiences with egg-containing injections. No clinical egg sensitivity developed.

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Two other children also developed dermal sensitivity with no evidence of clinical intolerance for egg. One child retained the reactivity fifteen months after influenza vaccination, and during this period additional tests and prophylactic doses of mumps vaccine failed to enhance the dermal sensitivity. The other child revealed a suggestively positive egg-white reaction after two 1-cc. injections of mumps vaccine. Both these children received a clinical allergic syndromes with influenza virus vaccine. There were 20 children, all sensitive to egg in varying degrees; these were divided into three groups: Group A — 6 patients, known to have been highly sensitive in the past but who had become clinically tolerant of egg; Group B — 7 children with residual dermal reactivity but no known clinical sensitivity to egg proteins; and Group C — 7 children who were egg-intolerant

TABLE 1. *Results of Inoculation With Egg-Containing Materials in 319 Children With No Previous Egg Sensitivity.*

TYPE OF VACCINE	NO. OF PATIENTS	NO. OF INJECTIONS PER PATIENT OF VARIOUS EGG-CONTAINING MATERIALS					TOTAL NUMBER OF EGG EXPERIENCES PER PATIENT	PERIOD OF TIME FROM FIRST INOCULATION	REMARKS ON EGG SENSITIVITY
		CHICK-EGG PROTEIN SKIN TESTS*	VACCINE TESTS†		PROPHYLACTIC INOCULATIONS‡				
			Influenza	Mumps	Influenza	Mumps			
								months	
Influenza and mumps	16	13	10	7	2	3 (0.1 cc.)	35	27	None developed egg sensitivity
Influenza and mumps	16	13	10	7	2	3 (1.0 cc.)	35	27	One child (LM) developed dermal egg sensitivity
Influenza and mumps	19	13	10	7	2	2 (0.1 cc.)	34	27	None developed egg sensitivity
Influenza and mumps	14	13	10	7	2	2 (1.0 cc.)	34	27	Three children (DS, JH, LC) developed dermal egg sensitivity
Influenza and mumps	16	13	10	5	2	0	30	27	None developed egg sensitivity
Influenza and mumps	5	13	5	4	0	0	22	27	None developed egg sensitivity
Influenza	77	11	10	0	2	0	23	13	None developed egg sensitivity
Influenza	32	11	0	0	0	0	11	13	None developed egg sensitivity
Mumps	26	2	0	7	0	3 (0.1 cc.)	12	12	One child (VS) developed dermal egg sensitivity
Mumps	29	2	0	7	0	3 (1.0 cc.)	12	12	None developed egg sensitivity
Mumps	21	2	0	7	0	2 (0.1 cc.)	11	12	None developed egg sensitivity
Mumps	27	2	0	7	0	2 (1.0 cc.)	11	12	None developed egg sensitivity
Mumps	21	2	0	5	0	0	7	12	None developed egg sensitivity

*Chick-egg protein tests: 0.02 cc. intradermally.
†Influenza-vaccine tests: undiluted 0.02 cc. intradermally; mumps-vaccine tests: diluted 1:5, 0.05 cc. intradermally.
‡Prophylactic vaccine injections: influenza vaccine, 0.1 cc. intradermally; mumps vaccine, 0.1 cc. intradermally, 1.0 cc. subcutaneously.

total of 34 reinjections during the twenty-seven months in which they were followed.

The fifth child received three inoculations of 0.1 cc. of mumps vaccine intradermally over a seven-week period. Six months after the first injection of vaccine an intradermal test injection with egg white elicited a suggestively positive response. This reaction was noted again when the subject was retested twelve months after the first inoculation. In the twelve-month period, during which she received a total of 12 reinjections, no clinical evidence of sensitization to egg protein developed.

It appears from this experience with nonallergic children that although mild dermal sensitivity may be acquired in rare instances none of our subjects became clinically sensitive to egg.

REPEATED INJECTIONS OF INFLUENZA VIRAL VACCINE IN EGG-SENSITIVE CHILDREN*

During the fall and winter seasons of 1947, 1948 and 1949 we injected children under treatment for clinically; they manifested symptoms of nausea or vomiting or both, abdominal pain, diarrhea, urticaria and asthma after the ingestion of egg or egg-containing foods.

RBC eluate vaccine. Two children (P. L., aged six years, and K. K., aged five years) from Group C were given a subcutaneous injection of 0.5 cc. of the RBC eluate vaccine. P. L. proved to be exquisitely sensitive, developing a generalized urticarial rash within one-half hour after the injection. No further vaccine injection was given. K. K., moderately sensitive to egg, tolerated this and a subsequent dose with no ill effects.

In view of the reactions observed in case P. L., we were unwilling to subject the more highly sensitive children of Group C to the risk of untoward allergic reactions from repeated injections of this relatively crude vaccine but instead selected children from Groups A and B.

Small doses (0.15 cc.) of vaccine, diluted 1:10 with saline, were injected into 7 of the 13 children of Groups A and B. They received from 2 to 20 injections, given once a week, together with 2 minims of epinephrine solution (1:1000)† in the same

*Two types of influenza viral vaccines were employed: RBC eluate vaccine, which consisted of virus concentrated by adsorption and elution from red blood corpuscles of chick embryo, and Sharples centrifuged vaccine, which contained virus concentrated by differential ultracentrifugalization. These were supplied by Dr. Herald R. Cox, Director of Viral and Rickettsial Research, Lederle Laboratories.

†The addition of epinephrine solution tends to delay the absorption of injected antigen and reduces the danger of untoward allergic reactions.

syringe. None developed any generalized reaction, and none showed any recrudescence of clinical egg intolerance during a one-year period of observation.

Sharples centrifuged vaccine. When this refined vaccine became available and when it was proved that the intradermal route was effective in stimulating adequate antibody titers,[3] we gave the more highly egg-sensitive children (Group C) doses of 0.1 cc. each, injected intradermally. Five of the 7 children of this group were given two doses, one month apart, and the procedure was repeated a year later. In each case a local reaction, consisting of a wheal with pseudopodia and surrounding erythema, ensued, but no systemic allergic response was noted. No increased allergic reactivity to the repeated vaccine injections and no enhancement of the clinical intolerance to egg was observed.

Ten children (Groups A, B and C) received Sharples centrifuged vaccine undiluted, 0.15 cc., administered subcutaneously with 2 minims of epinephrine (1:1000) at three-week intervals. These subjects, observed for one year with repeated tests, showed no enhancement of egg intolerance in the 2 clinically allergic children of this group and no recrudescence of clinical egg sensitivity in the remaining 8, who showed residual dermal egg sensitivity.

Repeated Injections in Children Allergic to Substances Other Than Egg

Allergic children, not sensitive to egg, were tested and given two subsequent prophylactic injections of from 0.15 to 0.5 cc. at one-month intervals. They were reinjected the following year. In a total of 120 children so treated, no clinical or dermal egg sensitivity was noted to have followed this procedure. This suggests that children allergic to substances other than egg are no more prone to develop hypersensitivity to egg from this vaccination than are nonallergic persons.

Comment

An exceptional case is reported by Stull[4] in an adult who, seven days after receiving a first inoculation of a crude equine encephalomyelitis vaccine, developed an urticarial reaction at the injection site. Two weeks after this, he received a second dose and had a local reaction one-half hour later. From this time on, he could not eat chicken or egg-containing foods without a gastrointestinal disturbance. Passive transfer tests with his serum were positive for egg yolk and chicken embryo but not for egg white.

Gold and Hampil[5] found that no sensitization followed repeated inoculations with equine encephalomyelitis vaccine in 69 normal persons. Bresler[6] reported that 302 normal subjects who were vaccinated twice with protamine-concentrated influenza vaccine at intervals of one year differed not at all, with respect to local and systemic reactions induced, from 308 persons who were vaccinated once in this period.

Plotz[7] attempted to determine whether cutaneous sensitivity follows subcutaneous injections of typhus vaccine in man. Cutaneous sensitivity developed in 9 of 150 vaccinated subjects. Despite this cutaneous sensitivity, all subjects sustained a subsequent subcutaneous injection of the full dose of typhus vaccine without systemic reaction.

In our own study, we found 5 subjects of 319 who developed a dermal sensitivity to egg. The fact that we found fewer cases than did Plotz must, we believe, be attributed to our use of a more refined vaccine than that employed by him. Although Plotz gave only three reinjections of vaccine, which some may criticize as too few to induce sensitization, the same objection cannot be leveled at our experiments. We gave as many as five therapeutic injections at four-week intervals and subjected our patients to as many as thirty additional experiences with egg-containing vaccines and test material over a period of twenty-seven months.

Serious allergy from the use of egg-containing vaccines has been encountered on first injection in those persons exquisitely sensitive to egg.[3] Striking as these cases were, it was equally striking that no allergic symptoms were induced in normal persons and in allergic persons not sensitive to egg and, furthermore, that no enhancement of allergy was encountered in those moderately sensitive to egg from repeated injections of these vaccines.

The frequent profound allergy and anaphylaxis that resulted from repeated therapeutic injections of horse antiserums was one of the most serious clinical allergic problems of the past five decades. Hooker[8] found that dermal sensitivity to horse serum was induced in about 27 per cent of normal persons from a single subcutaneous injection of toxin antitoxin containing only 0.0002 cc. of serum per cc. of toxin antitoxin. Park,[9] who corroborated this observation, expressed the belief, however, that systemic sensitization to horse serum from this source was a nearly negligible factor.

At first thought, one would expect allergy to result from a foreign protein injected repeatedly. Nevertheless, it is not surprising to us that clinical allergy was not induced from the repeated inoculations of egg-containing vaccines, in contrast to the situation with horse serum.

A spontaneously acquired immunity to egg protein, established by a continual contact with egg as encountered in the normal diet, may account, we believe, for the resistance to sensitization from this source. Egg protein cannot be regarded as a wholly foreign protein for the human subject in the same sense as horse serum. These pertinent considerations must be taken into account to explain what otherwise would appear to be a paradoxical situation.

Summary and Conclusions

In only 5, or 1.6 per cent, of 319 nonallergic children subjected to many repeated inoculations of influenza and mumps-virus vaccines did a dermal sensitivity to egg white develop. In no case was clinical sensitivity induced.

There was no enhancement of clinical sensitivity in egg-sensitive children repeatedly inoculated with crude and refined influenza-virus vaccines.

Egg sensitivity was not acquired after repeated therapeutic injections in 120 allergic children sensitive to substances other than egg.

Within the limits of our data, the hazard of sensitization from repeated reinjections of viral and rickettsial vaccines seems negligible. This, we believe, results from the resistance acquired from the habitual ingestion of eggs and egg-containing foods.

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SUCCESSFUL TREATMENT OF NEUROBLASTOMA

Report of Two Cases with Apparent Cures

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In 1864 Virchow[1] described a patient with neuroblastoma. Pepper,[2] in 1901, and Hutchison,[3] in 1907, described clinical features of the tumor. Rosendal[4] in 1942 collected some 300 cases, with few successful treatments. Lehman[5] in 1917 reported the first successful extirpation and in 1932 reported the fifteen-year survival of this patient.[6] In 1940 Farber[7] expanded the observations of Cushing and Wolbach;[8] he remarked that the tumors might undergo spontaneous hemorrhage with necrosis and disappear and that others might mature into benign ganglioneuromas. He stated that permanent cure, even after metastasis, was possible. Ladd and Gross[9] indicate probable cure of 7 of 32 cases (21.7 per cent). Wittenborg[10] reviewed 73 of the total of 143 cases observed in the Children's Hospital (Boston) up to 1949. There were adequate data to confirm the diagnosis in this group. He discussed the multipotentiality of these tumors, their curability even in the presence of metastasis other than to the skeleton and their treatment by x-ray alone, by surgery alone and by the combination of surgery and x-ray. Of 28 patients not treated there were 3 survivals after three years (10 per cent); of 12 treated by surgery only, there were 7, or 54 per cent; of 11 treated by surgery and x-ray, 6, or 54 per cent; and of 22 treated by x-ray, only 6, or 27 per cent. If the untreated cases are excluded, there were 19 of 45 surviving after three years, or 42 per cent. Wittenborg stressed the fact that cure after skeletal metastasis was unknown. He also stated that one could not be dogmatic concerning technic or the amount of radiation to be employed.

Thus in ten years there is progressive optimism shown in the treatment of patients with this tumor, Rosendal having found successful treatment rare in 300 collected cases, Ladd and Gross reporting apparent cure in 21.7 per cent and Wittenborg reporting apparent cure in 30 per cent of 73 cases (some untreated) but in 42 per cent of 45 cases that had been treated by surgery or x-ray or both.

A similar improvement in the results of treatment of embryonal carcinoma (Wilms's tumor) has been observed.

Case Reports

Case 1. R. D. was born on April 30, 1947, at the United States Naval Hospital, Chelsea, Massachusetts, weighing 7 pounds, 6 ounces. On the 5th day he weighed 7 pounds and was found to have a firm, movable, irregular mass about 4 cm. in diameter palpable in the left flank anterior to the kidney. X-ray examination revealed an area of homogeneous density. Two intravenous pyelograms, a barium enema with fluoroscopy, urinalysis and examinations of the peripheral blood were not significant. On May 14 operation disclosed a 6-cm. retroperitoneal tumor adjacent to the lower pole of the left kidney. The tumor was reddish brown, soft and friable; it was removed, apparently completely, together with adrenal gland, kidney and upper ureter. A small tear in the tumor capsule occurred. Microscopical examination at the United States Naval Hospital and the Children's Hospital (Boston) resulted in a diagnosis of neuroblastoma, normal kidney and normal adrenal gland.

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On May 31, x-ray radiation was instituted and was discontinued on July 9 when the white-cell count fell to 2900. The count rose, and radiation was reinstituted on July 23. A total of 1500 r was employed. The infant was discharged on July 29, 1947, aged 3 months.

On November 24, 1950, the mother reported that the child was well, that he weighed 39 pounds and had recently been examined by a physician, and that there were no abnormal findings.

CASE 2. V. J. was admitted to Mount Auburn Hospital, Cambridge, Massachusetts, in March, 1947. He was 7 months old and had been discovered to have an irregular conical mass in the left flank. Intravenous pyelogram was unsatisfactory. X-ray examinations of chest and colon were negative. On March 30, operation was performed, the descending colon mobilized and a firm, dark-colored tumor anterior to the left kidney was removed, together with the adrenal gland, which appeared normal. A single adjacent lymph node was also removed.

Convalescence was uneventful. The histologic diagnosis was neuroblastoma with lymph-node metastasis.

X-ray radiation was begun at the Children's Hospital on April 8, 1947; a total dosage of 4000 r was employed.

The child was examined on December 15, 1950 and was considered to be in good health. There was no evidence of tumor.

DISCUSSION

These cases are reported in order to encourage optimism in the treatment of malignant tumors of the young. About 80 per cent of neuroblastomas are observed within the first five years of life. Careful physical examination of the young at intervals of about six months is desirable for many reasons and is probably the only means by which early cancer detection is possible in the young. The dictum,[11] attributed variously to Dr. S. B. Wolbach and the late Dr. J. S. Stone, that all solid tumors of the young are malignant until proved otherwise is sound. Neuroblastoma is highly malignant, and not over 10 per cent of untreated patients will survive, but cure even after metastasis (other than skeletal) is possible. Surgery alone, x-ray alone or some combination of the two may be elected depending on the conditions, and a 42 per cent or better curability rate seems possible.

CONCLUSIONS

Two cases of neuroblastoma, one operated on at the age of fourteen days and the other at seven months, are reported. In both, complete surgical removal was possible. Both received postoperative radiation and both have survived more than three years.

The importance of carefully conducted physical examinations of the young and immediate operation when tumor is discovered are emphasized by these two cases, in which it is reasonable to assume that a cure has been effected.

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MEDICAL PROGRESS

SOME PRACTICAL ASPECTS OF CANCER PREVENTION (Continued)*

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CARCINOMA OF THE ORAL CAVITY

Incidence

In 1948, cancer of the buccal cavity and pharynx accounted for 4558 male and 1154 female deaths in the United States, representing 4.7 per cent of all male and 1.2 per cent of all female cancer deaths.[21]

A high incidence of oral cancer occurs in India.[65] Among 6077 patients at the Tata Memorial Hospital with neoplastic disease, 2179 had oral cancers. The primary sites included: base of tongue, 40.7 per cent; buccal mucosa, 18.5 per cent; tonsil, 15.1 per cent; anterior part of tongue, 13.6 per cent; palate, 5.3 per cent; alveolar ridge, 3.6 per cent; and lip, 1.6 per cent.

A high incidence of cancer of the hard palate is reported from the Vizigapatam district of India, where among 335 cancers of the oral cavity 52 involved the hard palate.[133] Although in the Bombay area the proportion of palate cancers to tongue is 1 to 9, the ratio in the Vizigapatam district is 6 to 1.[134] Cancer of the inner surface of the lower lip has been found particularly in the Bihar district of India, where the incidence is seven times as high as that observed in Bombay.[135]

British data reflect the average distribution as noted in western countries. Ledlie and Harmer,[136] reporting on 800 cases of cancer of the mouth, showed the following distribution: lip, 20.0 per cent; dorsum and border of anterior two thirds of tongue, 18.7 per cent; floor of mouth and inferior surface of tongue, 17.0 per cent; anterior faucial pillar and soft palate, 10.6 per cent; posterior one third (and whole) of tongue, 9.4 per cent; buccal mucosa, 7.4 per cent; lower alveolar ridge, 6.7 per cent; tonsil, 5.1 per cent; and hard palate, 5.0 per cent.

Oral cancer occurs predominantly in males. Martin found that for cancer of the lip and floor of mouth about 98 per cent were males and that for tongue, gum, tonsil, palate, cheek and pharyngeal-wall cancers the rate was between 80 and 90 per cent.[73] A similar sex ratio has been shown in the British literature.[136] The Indian data included 83.8 per cent males among 2179 cancers of the oral cavity.[65]

Swedish data, on the other hand, indicate a higher incidence of mouth cancer among females. Oral-cavity cancers seen at the Radiumhemmet Institute in Stockholm showed that pharyngeal-wall cancers included 60 per cent women, tongue 40 per cent, mouth 43 per cent and mesopharynx and hypopharynx 57 per cent women.[137]

Suspected Etiologic Factors

Most authors are in agreement that excessive use of tobacco plays a role in the causation of oral cancers. In 1915, Abbe showed that among 100 patients with cancer of the mouth, all had used tobacco in some form, including 13 tobacco chewers.[138] Taylor, in a report on 1014 cases of cancer of the mouth, found that only 4.3 per cent of 85 per cent of the men questioned had not used some form of tobacco.[139] Among the men questioned Friedell and Rosenthal found cancer of the buccal mucosa to localize most commonly at the point of greatest contact with the tobacco.[140] Orr showed that in 67 per cent of his cases in India the cancer occurred directly at the site where the betel-nut quid was held.[141] He suggested the betel-nut quid as a causative factor in the production of cancer of the mouth. Natives of New Guinea who chew betel-nut quid without tobacco, however, and Indians in the American Andes who chew cocaine leaves without tobacco fail to show a high incidence of mouth cancer. Hueper deduced from this circumstantial evidence that "extractives of cured and processed tobacco may be involved in the production of cancer of the mouth."[142]

Orr presented evidence to the effect that the degree of tobacco usage is directly related to the incidence of oral cancers. Among 100 cases of oral cancer and 100 controls without oral cancer, the following ratios were observed nonchewers, 2:34; occasional chewers, 9:31; persons who chew three to five times daily, 24:23; excessive chewers, 40:10; and those who retained the quid in their sleep, 25:2.

Kini and Subba-Rao attributed the high incidence of hard-palate cancer in certain parts of India to "chutta" smoking, in which, particularly among the poorer classes, the lighted end of the tobacco is held inside the oral cavity.[133] Khanolkar and Surybai, in describing this habit, suggested that since the temperature is only 65°C. near the lighted end, heat probably plays only a minor role in the causation of the cancer.[134] These authors attributed the high incidence of cancer of the inner surface of the lower lip in the Bihar district of India to the Khini type of tobacco use, in which tobacco is placed between the lower gum and the lip.

Mills and Porter concluded from their recent statistical study that smoking, — especially pipe

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and cigar smoking, — was of great significance in the etiology of buccal cancers.[50]

Swedish data also showed a high percentage of tobacco users in cancer of the oral cavity. Among cancers of the buccal mucosa, gingiva and alveolar process, 70 per cent used snuff and chewing tobacco; for cancer of the tongue, floor of the mouth and gum, only 24 per cent used these types of tobacco.[137]

Taylor placed great emphasis on dental hygiene as a causative factor. He suggested better dental hygiene to be one reason for the lower incidence of oral cancer in women.

Syphilitic glossitis has been thought to be important in the development of tongue cancer. Martin and his associates found a positive history of syphilis in 33 per cent of cases of cancer of the tongue, in contrast to an incidence of 4 per cent in a control group.[143] British data showed a positive Wassermann test in 16 per cent of 500 cases of oral-cavity cancer, in cancer of the tongue 28 per cent, of the buccal mucosa 20 per cent, of the palate 3 per cent and of the alveolar ridge 0.5 per cent. In a recent American report on 330 cases of cancer of the tongue, 21.8 per cent of the patients had positive serologic tests compared to 5 per cent in all hospital admissions.[144] Orr did not find syphilis to be significantly high in oral-cancer cases in India.[141] Swedish data showed an incidence of syphilis of 30 per cent for cancer of the tongue, whereas for cancer of the buccal mucosa, gingiva and alveolar process the syphilis rate was within expected limits.[137]

Ahlbom related the high incidence of oral cancers in Sweden to the Plummer–Vinson syndrome. Both diseases are more common among the poorer sections of the Swedish population than among the more privileged classes. Only 4 out of a series of 100 patients with oral cancer were private patients. Ahlbom attributed the syndrome to a dietary deficiency, particularly of iron, and suggested that it occurs frequently in women because of chronic blood loss during menstruation and pregnancy.[137]

Orr believed that diet plays a role in oral-cancer formation among his Indian patients. He found less mouth cancer in Indian population groups with an adequate diet than among those whose diet was considered to be unsatisfactory. He suggested that the diet of patients with mouth cancer is frequently low in vitamin A and in proteins.

Abels and his associates, in a well controlled study, found dietary deficiencies to be high in patients with oral leukoplakia, a condition that they found to improve occasionally when the patients were placed on large dosages of brewer's yeast.[145]

Experimental Evidence

Experimental evidence for tobacco is described in the section on lung cancer. There is no experimental evidence that a nonspecific irritant, such as a ragged tooth that irritates the mucous membranes, can induce neoplastic change in the absence of an underlying carcinogen. Possible dietary factors will be discussed under gastric cancers.

Evaluation of Present Knowledge

Etiologic factors in oral cancer are difficult to evaluate because complete surveys are not available. A full evaluation requires an investigation that would take into consideration all the possible etiologic factors, the specific location of each cancer and the histologic type of each neoplasm. Any investigation considering, for example, merely tobacco would not suffice.

Even with the data now at hand, the evidence incriminating tobacco is most suggestive, particularly if one considers the correlation between tobacco localization and primary site of carcinogenesis. The data on oral cancer, especially the Indian statistics, appear to leave little doubt that tobacco is carcinogenic to men and that the tobacco leaf *per se* is carcinogenic.

Available evidence on the incidence of syphilis in those with cancer of the tongue is striking. It might be of interest to investigate the type of therapy employed in these patients, particularly in reference to arsenicals. However, the special predilection of the tongue in cases of syphilis seems to place greater emphasis on syphilitic glossitis.

Evidence concerning poor dental and oral hygiene is difficult to evaluate as long as adequate control data are lacking. More information is required about type of dentures or bridges. This should, in particular, include information on the type of metal used in the dental repair. Poor oral hygiene, oral sepsis, ragged teeth and ill-fitting dentures may play a contributory role but probably not a basic part in the causation of oral cancer.

Little study has been made of the relation of food to oral cancer. A study involving dietary habits is difficult, due to erratic exposure to a large variety of foods. Further investigation relating to spices, alcohol intake and thermic factors of foods is needed. Particular attention should be paid to dietary deficiencies.

Preventive Aspects

From the evidence available, moderation in tobacco habits is of foremost preventive value. Dietary measures seem of prime importance, particularly for women in northern European countries. Successful reduction of syphilitic glossitis is an important preventive measure for cancer of the tongue. Adequate oral and dental hygiene is advisable.

Carcinoma of the Esophagus

Incidence

In 1948, esophageal cancer accounted for 2917 cancer deaths in men and 764 in women in the United States.[21] No significant increase in the incidence of this type of cancer in recent years is

recorded. A high incidence of cancer of the esophagus has been reported from China, where it accounts for about 50 per cent of all malignancies of the alimentary tract.[146] Cancer of the esophagus has been found to be more prevalent in northern areas of China than in southern and western areas.[147]

In the Dutch West Indies, esophageal cancer outranked cancer of the stomach.[148] In the British West Indies cancer of the esophagus ranked third in cancer autopsy statistics.[149] At the Tata Memorial Hospital in Bombay, 6.2 per cent of the cancer cases were of the esophagus, in contrast to 2.5 per cent of the stomach.[65]

The sex ratio has always been predominantly male, with reports varying from 3 to 10:1. This sex ratio would be even greater if only the middle and lower thirds of the esophagus were considered, since women have their greatest incidence in the upper third. In a series of over 1000 esophageal-cancer patients, Watson found 15.7 per cent women, whereas among the cervical esophageal cancers they made up 23 per cent.[150]

In Sweden, women have a particularly high incidence of cancer of the esophagus. Among 124 cases of hypopharyngeal (postcricoid) cancer, 74 per cent were women. Among 40 cases involving the lowest portion of the esophagus, 16 were women.[137] Similar data were given in a more recent Swedish report.[151]

Suspected Etiologic Factors

Craver, studying etiologic factors in esophageal cancers, found the following factors to be of importance in descending order: tobacco, alcohol, lack of water, poor teeth, lack of teeth and drugs (cathartics). The swallowing of hot food was not found to be a significant factor.[152] Watson suggested that poor dental hygiene and oral hygiene, poor mastication of food, thermal irritation and perhaps syphilis may be of etiologic significance.[153] Among 16 double primaries included in 771 cases of cancer of the esophagus collected by Watson, 14 were located in the intraoral region. This led Watson to the inference that similar etiologic factors may affect interoral and esophageal cancers.

In tabulating data on the use of tobacco, Ahlbom grouped together carcinoma of the pharynx, larynx and esophagus. Among 87 male patients, 99 per cent were users of tobacco, whereas among female patients only a few had smoked. The male group included 20 per cent pipe smokers, 64 per cent cigarette and cigar smokers and 16 per cent users of snuff or chewing tobacco.[137]

Among male patients, Ahlbom found a heavy alcohol intake in about one third of his cases but none in his female patients. He concluded that tobacco and alcohol play an important part in the etiology of pharyngeal and esophageal cancers. Cramer observed that up to 1925 cancer of the esophagus ranked second among the male population in Switzerland, but since then there has been a very extensive temperance campaign in that country and the incidence of cancer of the esophagus has markedly decreased.[154] Swiss statistics have shown a decrease of esophageal[155] cancer, but Schinz stated that the correlation of this finding to a decrease in alcohol consumption remains to be proved.[156]

Young and Russel found that occupations involving the handling of alcoholic beverages, such as those of brewers, innkeepers, beer bottlers and barmen carry a higher than expected incidence of esophageal cancer.[157] Dormanns' data on occupations of patients with cancer of the esophagus in Germany did not support this view.[158]

Kwan placed etiologic importance on chemical irritation, especially in the form of a strong vodka-like drink, paikon, containing 60 per cent to 85 per cent alcohol, which is used particularly among the poor farm population of China, where esophageal cancers are particularly common. This drink is rarely used by women. Thermal effects of food and drink are not considered to be responsible for the high incidence of esophageal cancers in Chinese men, since women eat as hot food as do men.[159] Korteweg pointed out that the Chinese sex ratio of esophageal cancer is not significantly different from western countries and that therefore etiologic factors should be suspected that apply to men throughout the world.[160] Wu and Loucks[147] believe that the high incidence of esophageal cancer among the populations of northern China may be due to the fact that the Chinese live chiefly on millet, maize and kaoliang, which they consider rougher food than rice, the main source of food in southern China. They suggested that the irritation caused by such food might be an etiologic factor. These authors also emphasized the possible significance of paikon, since 50 per cent of their esophageal-cancer patients drank paikon habitually, whereas among 200 control patients over the age of forty years only 12 per cent admitted to habitual intake of this drink. Paikon, according to these authors, is frequently consumed before it has undergone the aging process that helps to remove fusel oils and other irritant substances from its distillates.

Tomlinson and Wilson considered syphilis to be of etiologic significance in cancer of the esophagus.[149] Among 50 cases of cancer of the esophagus from the British West Indies, 52 per cent had definite evidence of syphilis as compared to 8.7 per cent found in routine autopsies. Watson's studies showed an incidence of syphilis of only 7 per cent, which he thought insignificant. In Sweden, Ahlbom found an incidence of 10 per cent of syphilis among the male cases, but none among the women. He allots only minor significance to syphilis.

Jacobsson cited evidence that a high correlation between sideropenia and cancer of the hypopharynx (30 to 40 per cent) has been noted in Norway and

Ireland, whereas it has not been observed in Denmark, France and Switzerland.[151] Ahlbom believed that the high incidence of esophageal cancer in Sweden is due to the Plummer–Vinson syndrome. Among 49 female patients with cancer of the hypopharynx, 37 had the Plummer–Vinson syndrome and 5 had anemia. Ahlbom has recently clarified his present point of view on the Plummer–Vinson syndrome and intraoral and esophageal cancers[161]:

> It can hardly be doubted that the iron deficiency plays an important role. We have therefore lately used the term Sideropenia which includes both the Plummer–Vinson cases and the cases without dysphagia (simple achlorhydric anemia). If a very careful history is taken and an expert x-ray examination of hypopharynx and upper esophagus is performed, it will be found that the majority of the sideropenia cases may be grouped as "Plummer–Vinson," but there will always remain a minority of cases with the same symptoms, except manifest dysphagia and corresponding objective changes in the lower hypopharynx, etc. Even the cases of this latter type run a definitely increased cancer risk, particularly perhaps regarding mouth cancer, whereas the real Plummer–Vinson cases are more likely to develop postcricoid carcinoma.

In regard to cancer distribution in European countries, Ahlbom wrote:

> In such countries as Italy and France, female mouth cancer is very rare, and probably the same can be said for the postcricoid cancers. It is difficult, however, to be sure about the postcricoid cancers, because numerous European statistics refer these tumours to cancer of the esophagus. Even so, if the frequency of sideropenia is estimated from the figures for female cancer in the oral cavity, pharynx, hypopharynx and esophagus, there seems to be a gradual increase from the south to the north.

Ahlbom suggested that a more careful search for signs and symptoms of sideropenia would reveal it more commonly among cases of intraoral and esophageal cancers, particularly in women.

Experimental Evidence

Experimental evidence on tobacco has been discussed. Dietary factors will be discussed under gastric cancer.

Evaluation of Present Knowledge

The incrimination of tobacco, as substantiated by most observers, seems quite suggestive. Tobacco, which is also believed to play a role in intraoral cancers, may form the basis for intraoral and esophageal double primaries. The apparent high incidence of esophageal cancer in India, where tobacco chewing is prevalent, also suggests a correlation.

Certain types of alcohol may be a contributory factor, but further proof is necessary. Evidence of hot foods, poor mastication, poor oral hygiene and certain types of foods is inconclusive. Data on syphilis are not conflicting, except for the data from the British West Indies, where a high correlation was found. In the Western countries, syphilis appeared to be of no major etiologic importance in relation to esophageal cancer.

The high incidence of esophageal cancer in the Orient and in the British and Dutch West Indies remains to be adequately explained, as does the relatively high proportion of cervical esophageal cancers in women.

The high incidence of hypopharyngeal and esophageal cancer in Swedish women appears to be closely related to dietary deficiencies associated with the Plummer–Vinson syndrome.

Preventive Aspects

From the data accumulated to date, preventive aspects of cancer of the esophagus seem to imply moderation in the use of tobacco. Improved dietary measures certainly do appear indicated, as evidenced by the Swedish data.

Carcinoma of the Stomach

Incidence

There has been no significant increase in the incidence of gastric cancer in recent years. The number of deaths in the United States from cancer of the stomach was reported as 25,228 in 1930 and 26,215 in 1948.[21, 68] Data for the latter include 16,321 males and 9894 females. There has been no recent change in this sex ratio. McNeer found an equal sex distribution among 501 patients with cancer of the stomach under the age of fifty.[162] In Europe, a particularly high incidence of gastric cancer has been noted in Holland. Two decades ago, gastric cancer accounted for 55.5 per cent of the total cancer mortality in Holland, as compared to 22.2 per cent for England and Wales. A slight decrease seems to have occurred in the mortality from gastric cancer in Holland during the past decade.[160] The Dutch data for 1950 (Holland's population is about 10 million) showed a mortality from cancer of the stomach of 2281 men and 1614 women. The British incidence of gastric cancer parallels that of the United States.[163] In England, cancer of the stomach has been found to occur more frequently in Northern Wales and northern parts of England, compared to most agricultural parts of Great Britain.[164]

A striking statistical difference has been reported from Java. Here both Malayans and Chinese have access to the same hospitals. Although gastric cancer is the second most common cancer among Chinese in Java, it is exceedingly uncommon among Malayan natives and is not recorded among the 10 most common cancers.[165] Bonne's autopsy group of 2748 Malayan men and 1137 women included only 1 case of gastric cancer. Similar differences between Chinese and Javanese have been found in East Sumatra.[166]

Among 28,015 deaths from cancer in Japan, 53.3 per cent were attributed to gastric cancer.[167] In Korea, gastric cancer ranks second in frequency to cancer of the penis in males and third after uterine and breast cancer in females and is about twice as common in males.[168]

In the United States, a relatively low incidence of gastric cancer is found in Alabama, Georgia, Texas, Mississippi and Louisiana.[169]

The problem of incidence of gastric cancer has been well discussed by Pack and McNeer.[170]

Suspected Etiologic Factors

Craver's work on the etiology of gastric cancer reported the following factors as of apparent significance, in descending order: poor teeth, lack of teeth, heat of ingested food or drink, irregularity of meals, lack of water, seasoning, cathartics, rapid eating, tobacco and alcohol.[162] Dunham and Brunschwig compared eating habits, the use of tobacco and the intake of alcohol and dental and oral hygiene of 40 gastric-cancer patients and 40 control patients. The most striking difference involved temperatures of food intake; 42.5 per cent of the gastric cancer patients, compared to 20 per cent of the controls, prefer well heated food. These authors suggested that this difference was not significant. They also reported that none of their other dietary findings were significant.[171]

Kennaway suggested that thermal factors may be of some significance in the production of cancer of the stomach.[172] He distinguished three types of cooking: multiple methods of heating, including roasting, baking, grilling and frying; slow cooking by hot ashes and hot stones; and boiling methods. The first type is most commonly used by the civilized world. It is assumed that such ways of cooking may not only give greater thermal irritation but that when certain food substances are cooked at higher temperatures, in particular fats, they may also be rendered carcinogenic.

Herbert and Bruske attempted to explain the higher incidence of gastric cancer among the Dutch as compared to the English. They found that the Dutch eat more bread, cheese and vegetables but less meat than the British. They also observed that the Dutch have a tendency to eat their food at a higher temperature, that they eat more rapidly and use more spices. Finally, they found the use of tobacco and the alcohol intake greater and oral sepsis more prevalent among the Dutch. The authors attribute some etiologic significance to these factors.[173] Although Korteweg agreed that the Dutch may have a greater preference for spices, hot foods and tobacco, he did not believe that sufficient evidence is at hand to incriminate any one of these specifically. Referring to the differences in Holland and England, he wrote: "An acceptable hypothesis for this difference in the prevalence of stomach cancer does apparently not exist."[160] Stocks, discussing the higher incidence of gastric cancer in the northern parts of England and Wales, suggested that this may be due to dietary differences, "either in the ingestion of irritant foods, or of substances in certain foods which tend to be preventive." He also noted that "fresh milk and vegetables seem to be very poorly represented in the diet of the bulk of the population of Northern Wales, and it is also probable that a predilection for the use of the frying-pan amongst them involves more gastric irritation."[164] His data also indicated that towns with a soft or very hard water supply have a higher incidence of stomach cancer than towns whose water supply is of intermediate hardness.[174]

Bonne and his associates set out to explain the striking difference between the Malayan and Chinese incidences of gastric cancer. In a careful study they were unable to establish physiologic differences in gastric function between the two races. The Malayans were more commonly vegetarians and ate no pork. These authors observed that other races that were equally vegetarian or also did not eat pork had the expected incidence of gastric cancers. Bonne and his co-workers also noted that the Malayans consume less alcohol than the Chinese.[175]

Experimental Evidence

In evaluating experimental cancer in mice, it must be borne in mind that the forestomach of the mouse is lined by squamous epithelium, which has been found to be more susceptible to cancer induction than the glandular epithelium of the stomach.

Davis and Ivy have studied the possible effect of thermal irritation on the induction of gastric cancer.[176] In their experimental work they were unable to show any malignant changes on the basis of thermal irritation, even though 2 of their dogs showed microscopical evidence of chronic gastritis.

Much experimental work has centered around the possible carcinogenic effects of heated fat. This subject has recently been reviewed by Lane, Blickenstaff and Ivy.[177] Peacock and Beck have been able to develop malignant tumors of the glandular stomach subsequent to the ingestion of preheated cottonseed oil. They obtained no tumors with preheated lard.[178] However, Burrows and his associates obtained spindle-cell tumors locally by subcutaneous injection of unheated lard.[179] Roffo heated lard to 350°C. and fed it to rats. He obtained malignant tumors of the glandular stomach after twenty-four months.[180] Lane and his co-workers could not repeat these results and speculate that part of their failure was due to the fact that only 12 of their animals survived twenty-four months. However, they were able to produce sarcoma by injecting lard subcutaneously. Hydrocarbons of known carcinogenic spectrum have so far not been identified in lard. Barrett, in a complete review of etiologic factors in gastric cancer, concludes that "no practical suggestion for cancer control programs is obtained from this review of dietary experiments in cancer."[181]

Evaluation of Present Knowledge

Available data on the role of exogenous factors in the production of gastric cancers are suggestive but still inconclusive. Part of this difficulty lies in

the obvious fact that eating habits are difficult to evaluate. Among the available reports and clinical impressions, the factor of thermal irritation seems to be the most constant. However, from the evidence at hand, the role of such irritation or the possibility that high temperature may form carcinogenic substances is difficult to evaluate.

In evaluating incidence data of gastric cancer it is well to consider the following conclusions by Pack and McNeer:

> It is our belief that the apparent gross variations in the incidence of gastric cancer in different parts of this country — and indeed throughout the world — do not reflect a genuine difference in susceptibility as much as variations in the general sociological plane. With the establishment of adequate medical facilities and education of the public in their early use, the disease is more frequently diagnosed and a higher morbidity rate recorded. At a common level of longevity, economic security, and public health education and opportunity, it is probable that the incidence of gastric cancer would be approximately the same the world over.

In comparing data on incidence we must also consider that a high incidence of certain cancers may account for a relatively lower incidence of others. Although it is certainly true that under similar medical and sociologic conditions the now apparent difference in incidence of gastric cancer in many population groups might disappear, there are still some areas in which the data on incidence are so striking, such as the relative frequency among Chinese and Malayans in Java, that at least some of the present differences should be investigated with great care.

Preventive Measures

Although thermal factors, heated fats, oral hygiene and certain dietary factors have been suspected to be of some etiologic significance, no specific preventive measures in respect to gastric cancer are apparent at this time.

Carcinoma of the Liver

Incidence

The autopsy incidence of primary cancer of the liver was .27 per cent in the United States and .14 per cent in Europe; its relative frequency to all other carcinomas accounted for 2.5 and 1.2 per cent respectively.[182] A significant increase in the incidence of liver cancer has occurred in Austria during the last decade.[183] No general significant increase, however, has been demonstrated.

Cancer of the liver is a common disease among the Bantu races of South Africa and among the Orientals. Berman reviewed 772 cancers among the miners of the Witwatersrand gold mines and of the patients of the Johannesburg Non-European Hospital, covering the period from 1925 to 1944, and found 86.6 per cent cancers of the liver.[182] Among the total Bantu population, the frequency of cancer of the liver constitutes 50 per cent of all cancer. It occurred 5.8 times as commonly among the East African Portuguese Bantus as among the South African natives. Cancer of the liver was more commonly found among Bantu mine workers than in the Bantus living in and around Johannesburg. In a recent report from the Baragwanath Non-European Hospital in Johannesburg, cancer of the liver accounted for only 5 per cent of 500 consecutive histologically proved neoplasms.[184]

Rosenberg and Ochsner did not find a significantly higher incidence of cancer of the liver in the American Negro as compared to the American white,[185] a point confirmed by Kennaway on reviewing the American literature.[186] The tabulation of data by Berman shows the following percentage relations of liver cancer to all other neoplasms in Oriental races: Javanese, 41.6 per cent; Chinese, 33 per cent; Filipino, 22 per cent; Indian, 17.5 per cent; and Japanese, 7.5 per cent.[182]

In Korea, it is the fourth most common cancer in males.[168] Wilbur and his associates have reported a significantly high incidence of cancer of the liver among Chinese in San Francisco. Among 49 cases seen at Stanford University, 19 per cent occurred among Chinese.[187] Similarly, a report from Vancouver noted that among 139 autopsies on Chinese patients, 10 had primary cancer of the liver whereas among 1828 whites only 2 were found.[188] Cancer of the liver occurs more commonly among males than among females in all reports. A review of 300 cases by Greene showed a sex ratio of 6:1.[189] Of 157 cases from Dakar, 94 per cent were in males.[190] The percentage of 86.6 per cent quoted above for Bantus consisted only of males, chiefly because the mining population that this particular report describes is predominantly male. Female Bantus show an incidence of 5.1 per cent. Primary cancer of the liver among Javanese males accounted for 79.3 per cent and in females 6.2 per cent.[182] In Korea, it is four times more common among males.

Suspected Etiologic Factors

A recent excellent review by Rosenberg and Ochsner and the detailed monograph by Berman have well summarized the problem of carcinoma of the liver.[182, 185] There is general agreement that nutritional factors play a prominent role in its production. Berman found cirrhosis in all his cases. Hoyne and Kernohan found cirrhosis in 75 per cent of the cases in the hepatocellular carcinomas and 18 per cent among the bile-duct type[191] whereas the data of Rosenberg and Ochsner on the same two types indicated an incidence of 86.2 per cent and 38.4 per cent respectively. A tabulation from the literature by Berk and Lieber of 1073 cases of primary cancer of the liver showed cirrhosis to be present in 61.3 per cent of cases.[192]

A correlation between cirrhosis and primary cancer of the liver has also been drawn from the in-

cidence of primary liver cancer in patients with cirrhosis. Berk and Lieber found 45 primary liver cancers (2.8 per cent) among 1989 cases with cirrhosis.

Hemochromatosis has been suspected to lead even more commonly than cirrhosis to cancer. Sheldon reported 5.8 per cent primary carcinoma of the liver among 345 cases of hemochromatosis.[193] Berk and Lieber, in reviewing 436 cases of hemochromatosis, found, primary cancer of the liver in 7.3 per cent. Warren and Drake found the autopsy incidence of liver cancer in patients with hemochromatosis to be 18.9 per cent.[194] Nutritional deficiencies have been noted among the Bantus. They live primarily on maize, with inadequate additions of fermented cow's milk and vegetables. The infants in the rural districts receive very little fresh milk. These diets are especially low in protein and vitamins.[195] Rusch and Baumann postulated that such diets might be lacking in factors essential for defensive mechanism against carcinogens.[196] Berman postulated that the lower incidence of liver cancer among the East African Portuguese, as compared to the Bantus, might be due to the fact that the Bantus live in tropical areas and have less milk, because in this region the tsetse fly is endemic and this factor affects the cattle. In these regions only small supplies of goat's milk are available.

Deficient diets are also held as a chief reason for the high incidence of cancer of the liver among the Orientals.

Several exogenous factors are thought to act as carcinogens for cancer of the liver. Katata suggested a correlation between *Schistosoma japonicum* and liver cancer.[197] Pirie found *S. haematobium* ova in 7 out of 36 primary-cancer patients in the Bantus.[198] Berman, however, noted that even though 24 of his patients had *S. haematobium* ova in the bladder none were found in the liver. He did not consider helminth infections of great significance in this regard. This belief seems to be borne out by data from Egypt, where no relation between cancer of the liver and bilharziasis has been found. Among 340 cases of cirrhosis based on bilharziasis only 4 cases of liver cancer were found.[132]

Alcohol has been suspected to play a role. Many Bantus drink alcohol from early childhood. The most commonly used drink is Kaffir beer, which contains between 2 and 4 per cent alcohol. The Portuguese drink "Marewu," which contains less than 1 per cent alcohol. These drinks are apparently regarded as food and are consumed throughout the year. Some intoxicating drinks made from fruits are also used, but data on frequency of their use is not recorded. In Rosenberg and Ochsner's series, alcoholism was found in 18.2 per cent. Spatt and Grayzel noted no significant alcohol intake among their patients with cancer of the liver.[199] Wilbur and his group noted a considerable alcohol intake in 22.5 per cent of their cases.[187]

Syphilis has been thought to play some role in the production of cancer of the liver, a belief that has not been confirmed by large-scale data. Rosenberg and Ochsner found 6 cases of syphilis among 55 patients with liver cancer.

There has been speculation about the possible carcinogenic effect of food-coloring substances. Zaribnicky[200] and Zeitlhofer[183] placed particular emphasis on the carcinogenic properties of butter yellow. It has been held that the incidence of primary cancer of the liver in Japan was based at least to some extent on the use of food-coloring dyes in margarine. Miyaji, however, writes that margarine is not a popular food in Japan and that the high incidence of cancer of the liver is probably due to rice diets and associated protein and vitamin deficiencies.[201] Druckrey cited a case of cancer of the liver in the wife of a dairy owner; she ate much highly colored butter during the war years. He stated, however, that because of the usual latency period in cancer the possible carcinogenic effect of butter yellow cannot be evaluated on human evidence at this time. Yet he emphasized that "because butter yellow has been proved to be carcinogenic to animals, its use should be prohibited in men under all circumstances, because we cannot wait for the results of the human experiment."[202]

Experimental Evidence

Experimental data have recently been well reviewed by Sugiura.[203] Sasaki and Yoshida, using aminoazotoluene, were the first to produce cancer of the liver in rats in 1935.[204] In 1937 Kinosita was able to produce it with butter yellow "P-dimethylaminoazobenzene."[205] Together with butter yellow, he fed rats a diet consisting of unpolished rice and carrots.

Several factors have been found that may accelerate formation of cancer of the liver among which biotin, pyrodoxin and inositol are of particular interest. Gillman and his co-workers succeeded in producing severe liver damage but no primary cancer of the liver in rats fed with a plain maize diet, such as is used by the Bantus.[206] Cook, Duffy and Schoental recently induced cancer of the liver in rats after feeding with alkaloids of *Senecio Jacobaea*, which the South African Negroes use for treatment of a large variety of diseases. These authors believed that the alkaloid may contribute to the high incidence of cancer of the liver among these Negroes.[207]

Numerous experiments have shown that the addition of certain dietary substances will retard the induction of liver cancer, particularly by the addition of yeast, rice-bran oil, casein, riboflavin, wheat and fresh cow's milk. Sugiura and Rhoads showed that liver cirrhosis produced by butter yellow can be successfully treated by a rice diet containing 15 per cent yeast or dried milk. These

experiments indicate that once tumor formation has begun it is irreversible.[208]

Evaluation of Present Knowledge

For many years the high incidence of cancer of the liver in certain parts of the world was attributed to particular racial susceptibilities. This concept is no longer tenable in view of the statistical and experimental data available. The fact that its incidence is high among some Bantu groups although not among others should in itself be sufficient evidence for regarding some exogenous factors as responsible for the production of many of these cancers. The apparent prevalence of cancer of the liver in Chinese in the United States does not necessarily mean racial susceptibility but may be due to dietary habits. More complete data on both birthplaces and dietary habits of these Chinese is desirable.

Helminth infection does not seem to play a significant role in the production of primary cancer of the liver, in view of Berman's findings and because of the relatively low incidence of primary cancer of the liver in Egypt, where schistosomiasis is endemic. Furthermore, helminth infections are not endemic in Java, where cancer of the liver is also reported to have a very high incidence.

There is no good evidence that syphilis is of major significance in the induction of cancer of the liver. The evidence against alcohol is also indefinite, although cancer of the liver is related to the incidence of cirrhosis.

Suspicions directed against food-coloring dyes, on the basis of experiments on animals, are difficult to substantiate from an epidemiologic point of view. However, Druckrey's point, — that we should not wait for human evidence and that the use of the particular food-coloring substance found to be carcinogenic to animals should be avoided, — is well taken.

The development of primary cancer of the liver seems to involve dietary deficiencies — particularly those inadequate in protein and vitamin B complex. Such deficiencies are of similar importance in cirrhosis and may explain the high incidence of cancer in patients with cirrhosis. It is difficult to state whether deficient diet alone is sufficient to induce liver cancer or whether carcinogens are required in addition, be they exogenous or endogenous.

Preventive Measures

The data presented leave little doubt that improved dietary measures could lead to a drastic reduction of primary cancer of the liver. Such a goal might possibly be obtained by adding vitamin B complex to the diets of those races in which primary liver cancer is prevalent. Such a project, although difficult to evaluate in man, should be attempted in those regions where a high frequency of liver cancer prevails. In addition, butter yellow should not be used as a food coloring, despite the fact that human evidence in respect to this dye is still inconclusive. The use of butter yellow for food coloring has been prohibited in the United States. Two other dyes (yellow AB and yellow OB), which have been shown by Sugiura to be noncarcinogenic to rats, are permitted. In the last analysis, the best weapon against primary cancer of the liver is adequate nutrition throughout the world.

(*To be concluded*)

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COLLEGE OF OSTEOPATHIC MEDICINE AND SURGERY MANHATTAN KANSAS

MEDICAL INTELLIGENCE

MIGRAINE*

L. M. D.

I AM a sufferer from migraine; so were my mother and grandmother and three of my sisters. My eldest daughter, now twenty-one, has had migraine since she was eight years of age. This hereditary factor, I believe, is the foundation of our affliction. I do not, of course, mean that one inherits headaches. But given a hereditary craniocerebral vasolability, the wear and tear of daily living can produce in such a person periodic headaches that at times may even rise to the intensity of pain often suffered by patients who harbor brain tumors.

My memory of the onset of my headaches is not very clear. The earliest attacks that I can recall took place while I was in high school. The present pattern of the paroxysms, however, did not become established until after my graduation from medical school. I remember distinctly many occasions of irregular meals and insufficient sleep, — as, for example, while "grinding" before examinations, which nowadays would certainly precipitate an attack, — yet I recall no associated headaches. As I grew older and my activities became individual rather than as part of a class, the headaches, or at least my memory of them, became more prominent.

In my case, the attack is usually initiated by a mild but persistent ache in one temple that may be on either the right or the left side. This grumbling ache may last several hours, even half a day, and sometimes fluctuates in intensity, although it usually increases steadily until the peak is reached. In this early stage I believe I can frequently abort the attack by taking four tablets of aspirin (1.25 gm.), but since the ache may disappear spontaneously, without the medication, or since it may reach a crescendo in spite of the aspirin, I feel uncertain about the efficacy of this treatment.

I have built up a rather elaborate mechanism of ignoring the early stages of an attack; this consists of redoubled effort at concentration on any work that I may be doing. If the pain increases, however, the effort is costly and may become quite grim, accompanied by setting of the jaws — which eventually only serves to increase the pain. This system usually fails in the end, but it does succeed in delaying the climax of the attack, since on other occasions, when the absence of pressure from work makes it possible to recline in a chair or lie down, the greatest intensity of an attack is reached much earlier but may be less severe.

Sometimes the early stages of an attack occur during the morning just prior to a scheduled brain operation. My operations usually begin at 1:30 in the afternoon. When this occurs, I tie the sweatband that I wear around my head during operations more tightly than usual. This, plus the firm contraction of the jaw muscles, makes it possible to go through a three- or four-hour operation, during which the necessary precise and meticulous maneuvers become more precise and more meticulous than ever, as if to show the demon of migraine who is the boss. But the payoff comes when the operation is over. As soon as the sweatband is released and my jaws drop open from fatigue, great swollen humming pulses of pain streak through my temples and the base of my head. My face turns greenish pale; I break out into a cold perspiration; my hands and feet feel cold and I feel chilly all over. Even a dim light in the room sends additional shafts of pain through my eyes. My stomach seems to turn over, and I wish that I could vomit but usually cannot.

The effort to bathe and dress, dictate the operative note, discuss the operation with my assistants and often even make ward visits, seems almost superhuman. At last the strife is over. I crouch in a corner of a taxicab to be driven home and finally crawl under the blankets without putting on the lights and often without undressing. Sleep is difficult to induce; localized pressure of my head against the pillow causes additional pain. I occasionally obtain some relief by putting the pillow on my head instead of under it and holding it down tightly with both hands. Sleep comes at last, and a forgetting — until the next time. Fortunately for me, these severe attacks come quite rarely, and their coincidence with an operation is even less frequent.

On awakening I feel unsteady, weak and hungry but as if purged of something evil. I usually pass a large quantity of colorless urine. Breakfast has a remarkably restorative effect, and the world becomes bright and cheerful. All irritability is gone, and being calm, patient and understanding no longer seems an impossible task.

Like most victims of migraine, I have speculated a good deal about the factors precipitating an attack. At various times I have thought that certain foods such as green peppers or fat fish, especially mackerel, are contributing causes. Among other things, constipation, insomnia, alcoholic drinks and irregular meals may light the fuse that eventually leads to an explosion.

But the underlying causes, I am convinced, are anxiety and tension. This relation, however, is not as simple as a problem in geometry — that is, a period of anxiety and tension, *ergo* headache. The

*This essay, presented here in a slightly abridged form, will appear in the forthcoming book *When Doctors Are Patients: Autobiographical Sketches of Disease by Physicians*, edited by Max Pinner, M.D., and Benjamin F. Miller, M.D., to be published by W. W. Norton and Company in 1952.

anxiety and tension do not themselves set off an attack but give rise to a series of events that terminates in one. It may be a period of several major and difficult operations and of concomitant anxiety about the success of the next day's operation as well as the postoperative course of today's and yesterday's surgical patients. Thoughts race through my mind, reviewing the steps of tomorrow's operation and anticipating whatever complications may arise. At the same time I am mentally checking the significance of those symptoms that the postoperative cases are showing and whether they are being adequately met. The night deteriorates into a marathon of tossing and turning. Then the alarm clock finally rips into the peace of sleep attained, after complete exhaustion, during the last few hours before morning. On awakening, unrefreshed, the first dull ache in one temple gives warning of things to come. Breakfast is a desultory affair. The habitual elimination does not materialize. Irritability, which if unrestrained would estrange the whole world, must be controlled, and in spite of large doses of aspirin the course of events may not be interrupted.

What is difficult to explain, however, is that an attack by no means necessarily follows every occasion of anxiety concerning work or other things, even if it produces insomnia. It nevertheless is also true that when things run smoothly for months at a time I sometimes forget that I ever had a headache.

The situation is further complicated by the occurrence of headaches not at the time of tension but often when the tension is over — or perhaps when anxiety and tension are anticipated. My home is in Connecticut, and I work in New York City. My habit is to spend Monday to Friday in the city and go home for the weekend. On Saturdays and Sundays I read, relax, garden, do a little sculpturing and keep in touch with the hospital only by one or two telephone calls. These weekends are a restorative without which it would be difficult to keep up this pace. However, at about 9 p.m. on Sunday night the sense of relaxation disappears. I go upstairs and lay out my "city" clothing, fill my bag with supplies for the coming week and retire early. I am often unduly annoyed with my wife if she happens to make a social engagement for Sunday evening, out of fear that the visit will last past my bedtime. And I am irritated by the family if we spend Sunday evening at home and youthful spirits prolong the music and laughter, which at other times I enjoy, past 10 o'clock. On Friday and Saturday nights I sleep like a top, but on Sunday night I frequently sleep poorly. I rise early to catch a train, but the alarm clock is set at least fifteen minutes earlier than necessary, and I reach the railroad station that much earlier than necessary. In spite of this I have to control a rising sense of annoyance with my wife if she seems to me to be slow in getting ready to drive me to the station. On such mornings my head feels heavy and full, and the telltale little gnawing ache appears in one of my temples to signal the dawn of a "blue Monday."

Still another variation occurs on vacations. Preparation for going on a vacation requires considerable planning — such, for example, as arranging operation schedules to leave no recently operated or very sick postoperative cases behind, even though my associate is completely competent and reliable. This, plus routine duties, plus whatever personal matters have to be attended to, increases the load of work considerably. Yet I do not recall any notable attacks during such periods. On the other hand, once the vacation is started I have gone on trips lasting a month or more and had some degree of headache every day of the entire period, although they seldom rise to the level of a real migrainous attack.

There is no doubt in my mind that the migraine victim belongs to a personality group that although varying in detail from person to person nevertheless constitutes a "type." In his excellent and important book *Headache*, Wolff analyzes these traits one by one; when I read about his cases I suddenly had a feeling that all these persons were more like me than were some of my own kith and kin. One of the outstanding characteristics of this group, according to Wolff, is "perfectionism." There is no doubt that "perfectionism," however, valuable as it is to the world, is a burden, especially if it is accompanied by migraine.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38141

PRESENTATION OF CASE

A forty-eight-year-old woman was admitted to the hospital because of chills and fever.

For one month prior to entry the patient had noted tiredness and anorexia. Three days prior to admission she developed a pounding frontal headache and was noted to have a low-grade fever. The day before entry she had a shaking chill followed by a temperature of 104°F., severe malaise, headaches and a vague ache in the muscles.

The menopause had occurred two years before admission, but one month prior to entry she had had an episode of vaginal bleeding of a few days' duration, with irregular vaginal spotting since that time; she had taken stilbestrol daily because of hot flashes from six months until ten days prior to entry. Her father and one sister died of tuberculosis, and a brother died of Hodgkin's disease.

The temperature was 102°F., the pulse 100 and the respirations 20. The blood pressure was 150 systolic, 70 diastolic.

Physical examination was negative except for slight but definite tenderness on deep palpation in the right flank.

The urine had a specific gravity of 1.012 and gave a ++ reaction for albumin; the sediment was loaded with clumps of blood cells. Cultures of the urine grew abundant *Escherichia coli*. Examination of the blood showed a white-cell count of 16,000, with 77 per cent neutrophils and a hemoglobin of 13.2 gm. A nonprotein nitrogen was 16 mg. per 100 cc. Roentgenograms of the chest showed some prominence of the left side of the heart shadow; the heart did not appear to be enlarged and the lung fields were clear. Vaginal smears were "doubtful" for malignant cells.

Treatment with sulfadiazine resulted in a prompt subsidence of the symptoms and clearing of the urine. A dilatation and curettage was performed; the pathological report was atrophic endometrium. An intravenous pyelogram performed a few days before discharge was negative. She was discharged on the twelfth day.

Second admission (three years later). In the interval the patient had felt well; there had been no further vaginal bleeding. Two weeks before admission she noted that she tired easily. One week prior to entry she began to note chilly sensations and the following day she had a frank shaking chill. Her physician found 10 to 20 white cells in the urine and prescribed a triple-sulfonamide preparation. The urine became free of pus cells on this therapy, but she developed headache, vague generalized backache, profuse sweats, chilly sensations, paroxysms of fever up to 102°F. and mild shortness of breath on exertion, especially when the temperature was raised. There had been no cough, chest pain or urinary symptoms.

Physical examination revealed a middle-aged woman who did not appear ill. The neck veins were full. The lungs were clear. The heart was normal in size and the heart sounds *per se* were normal; over a clearly defined area from the xiphoid to the apex there was a harsh loud adventitious sound, which was variable in timing but was mostly systolic. This sound was heard only when she was in the supine position, disappearing when she sat up, and its intensity was diminished by deep inspiration. Examination of the abdomen and pelvis were normal. One Heberden node was present on the left little finger.

The temperature was 102°F., the pulse 100 and the respirations 20. The blood pressure was 140 systolic, 70 diastolic.

A urine of specific gravity 1.012 was normal. Examination of the blood showed a white-cell count of 6000, with a normal differential, and a hemoglobin of 11.4 gm. The erythrocyte sedimentation rate was 20 mm. in 15 minutes, 46 mm. in 30 minutes and 60 mm. in 60 minutes. The nonprotein nitrogen was 28 mg. per 100 cc., the serum chloride 92 milliequiv. per liter and a fasting blood sugar 116 mg. per 100 cc. Agglutination tests for typhoid and undulant fever were negative. A blood Hinton test was negative. Roentgenograms and fluoroscopic examination showed marked enlargement of the heart without characteristic configuration (Fig. 1). The amplitude of the pulsations of the heart was diminished; there was no appreciable change in the size of the heart on the Valsalva and Mueller tests. There was some prominence of the superior vena cava and azygos veins. The lung fields were clear. An electrocardiogram showed a normal rhythm at a rate of 100, a PR interval of 0.16 second, a QRS interval of 0.08 second and a tendency to low voltage. The T waves were upright in Leads 1 and AVL and flat in Leads 2, 3, AVF, V_1, V_2, V_3, V_4, V_5 and V_6.

In the hospital the patient continued to have a temperature ranging from 100 to 101°F. with spikes up to 103°F. She had a few brief episodes of acute

dyspnea usually associated with a rise in temperature; the longest of these lasted four hours. Digitalis and Mercuhydrin had no significant effect; Chloromycetin also had no noticeable effect and had to be discontinued after four days because of severe nausea and vomiting. The physical findings remained unchanged, with the addition of the following: blood-pressure drop of 10 mm. with deep inspiration; suggestion of gallop rhythm at the apex and of a paradoxical pulse; heart sounds more distant than at admission; neck veins pulsating at a

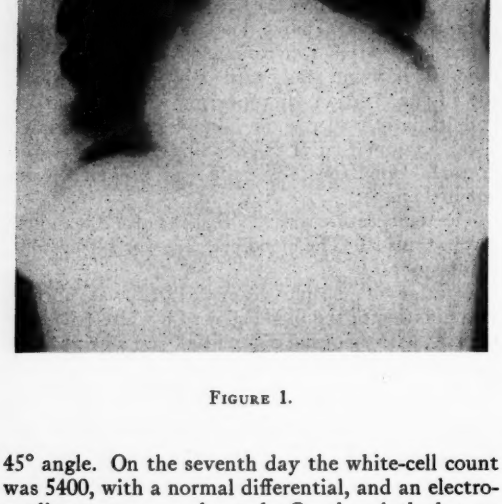

FIGURE 1.

45° angle. On the seventh day the white-cell count was 5400, with a normal differential, and an electrocardiogram was unchanged. On the ninth day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EARLE M. CHAPMAN*: "Adventitious" — I had to go to the dictionary to refresh my memory about this word; it is defined as "added extrinsically, not essentially inherent, acquired, accidental, casual." This word, which is used in many ways, is the most important choice in this whole physical examination.

I should like first to look at the x-ray films.

DR. STANLEY M. WYMAN: The first two films, taken during the original admission to the hospital, show no evidence of intrinsic pulmonary disease. The heart shadow may be a little prominent in the left ventricular portion, but that is not very striking. The aorta is not remarkable. The bones appear well preserved, and I see no other evidence of disease. The films taken in the second admission demonstrate a great change in the size of the central heart shadow, which is now rather rounded and shows loss of normal geographic contours (Fig. 1). According to the fluoroscopist, there was definite diminution of pulsation of the margins of this shadow. There is no evidence of fluid in the pleural spaces and nothing that I can recognize in the lungs themselves. The superior vena cava and azygos vein are more prominent than usual and are certainly more prominent than on the original examination.

DR. CHAPMAN: Is there any evidence of calcification around the heart in any of those films, especially along the diaphragmatic surface?

DR. WYMAN: No; none that I can see — and according to the fluoroscopist's report it was not seen at fluoroscopy, which is the best time to make this observation.

DR. CHAPMAN: Isn't it a medical aphorism that the absence of pulsation in the heart with clear lung fields is diagnostic of pericardial effusion?

DR. WYMAN: I think that is the most probable explanation for this situation.

The films taken from the pyelogram show no significant intrinsic disease that I can recognize. The left kidney may be rotated on its long axis.

DR. CHAPMAN: Do you see any calcification in the region of the kidney?

DR. WYMAN: No; there is no evidence of renal or adrenal calcification. I am not impressed with the pyelogram.

DR. CHAPMAN: And these little areas in the lung out here — you do not interpret them as an early lesion of tuberculosis on the early films?

DR. WYMAN: I think it may be a tiny scar but not a significant one.

DR. CHAPMAN: Does it show on the second films?

DR. WYMAN: Perhaps, but at any rate I would not attach any significance to it. It has not changed or become worse.

DR. CHAPMAN: In reconstructing the situation I can only link up the first hospital entry with the entry three years later in so far as one has to suspect the possibility of a tuberculous lesion in the kidney. Since the patient had blood in the urine and evidence of infection, which evidently responded to sulfadiazine, the supposition is that there was a bacterial infection from which she recovered completely. The vaginal bleeding at the time, I assume, was due to stilbestrol therapy. I cannot link the first entry with the second.

When I come to the next problem of her departure from health, it seems clear to me, and the x-ray films confirm it, that she had pericardial effusion; pericarditis with effusion can be caused by a number of

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things. The one thing that I was rather surprised by was that there was not a better clinical description of the state of the venous pressure — only the remark that the veins were filled and pulsated at a 45-degree angle. It would have been helpful to know more about this. The other things I assume are absence of enlargement of the liver and spleen, and of ascites.

DR. REED HARWOOD: At the time she was operated on, she had no ascites or, as far as I could make out, enlargement of the liver or spleen.

DR. CHAPMAN: A total protein was not included at that time; I take it that no total protein was done on the patient before operation.

I am faced with the diagnosis of a rather acute process with pericardial effusion and a spiking fever; what are the possibilities? The commonest basis is a tuberculous lesion; the next, rheumatic fever. I cannot find anything in the history suggesting that this patient had rheumatic fever, and likewise the absence of precordial pain and other signs do not fit with the patient's having had a coronary thrombosis.

Subacute bacterial endocarditis also seems to be ruled out, although it would have been nice to have a blood culture from this patient.

DR. BENJAMIN CASTLEMAN: The blood culture showed no growth.

DR. CHAPMAN: That would tend to rule out acute bacterial invasion by the usual type of organism that causes pus formation.

Malignant tumors? I noted that there was Hodgkin's disease as well as tuberculosis in the family history; therefore one thinks of the possibility of this being a lymphoma in the lung root. In the description of the x-ray films it seemed that the left side of the heart was rather large; in your interpretation, Dr. Wyman, you mentioned no suggestion of nodes in the hilum.

DR. WYMAN: No; I do not see them.

DR. CHAPMAN: I do not either, so I shall discount lymphoblastoma.

Another condition that might cause this is disseminated lupus erythematosus, but there was no description of skin lesions or multiplicity of effusions in joints that would lead one to suspect this. There was one Heberden node in the little finger; that is a very tiny "red herring." Dr. Walter Bauer and Dr. William Clark[1] described a pericarditis in 12 per cent of 62 cases of rheumatoid arthritis. I did some multiplying; that is seven and a half patients. Dr. Ropes, would you tell us how many patients in your series had pericardial effusion?

DR. MARIAN W. ROPES: The incidence of effusion was low — approximately 6 per cent. The incidence of pericarditis was very high, in our series and in another autopsy series going up to 44 per cent.

DR. CHAPMAN: Why did she have pericarditis with effusion and this appearance? One disease that can simulate this picture closely is mitral stenosis; I must mention that briefly. In mitral stenosis, the left-ventricular filling defect, — the impedance of filling of the left ventricle, — is due to the tight mitral valve; in chronic constrictive pericarditis, the insufficiency of filling of the left ventricle is on the basis of fibrosis about the left ventricle. I think it was Dr. White[2] who reported in 1948 that fibrosis can involve the groove between the left auricle and the left ventricle. Of course, when the groove is decreased the diastolic capacity of the ventricle is decreased, producing a high back or pulmonary pressure that can be measured by the catheter. The same results are obtained from catheter studies in this condition as are found in mitral stenosis. Were catheter studies done?

DR. CASTLEMAN: I do not believe so.

DR. CHAPMAN: I do not believe anything here suggests that she developed mitral stenosis between the ages of forty-eight and fifty-one, but I must mention it in passing.

That brings me back to what I think is the most likely diagnosis — pericarditis with effusion. The "adventitious" sound I should call a friction rub.

The next test of the situation is: What was the operation and why was it done? It is significant that the electrocardiographic changes were consistent with pericarditis and in fact suggested an extension of the process into the superficial layer of the myocardium, not with true infarction of the myocardium. The patient was going downhill and I think had the signs of cardiac tamponade — Beck's classical triad: rising venous pressure, falling arterial pressure and a small quiet heart. In a way she had this. Dr. Edward D. Churchill and Dr. Soutter probably would object to the phrase "a quiet heart"; Dr. Churchill says he almost never hears it. The neck veins finally became pulsating at an angle of 45° and the heart sounds were more distant — the heart was not smaller but it was quieter, so she must have developed the picture of cardiac tamponade, which indicated an exploratory operation.

What studies would help to make the diagnosis? An angiocardiogram might have helped. Was one done?

DR. CASTLEMAN: No.

DR. CHAPMAN: Where was the incision made and what was done? I suppose I should guess about that.

DR. CASTLEMAN: No.

DR. CHAPMAN: Well, let me; I would like to. The surgeons may have put a needle in, taken out some fluid and squirted in streptomycin. As I understand it, aspiration and pericardiectomy are new methods for diagnosis and treatment of pericarditis with effusion. They may have suspected that she was forming fibrosis and developing a chronic constrictive pericarditis, although there was no clinical

history of it; this exploration might have been designed to relieve the picture of cardiac tamponade due not only to fluid accumulation but to a rapidly developing fibrosis. This is supported, perhaps, by the electrocardiographic evidence. There are several approaches used in that operation; Blalock[3] would make an incision in the fourth interspace and remove the fourth and fifth costal cartilages and really expose the heart so that the possibility of fibrous rings about the groove between the left auricle and ventricle as well as the right side could be explored. In their experience they have sometimes had to go back and do both sides. There is no evidence in the x-ray films to support this situation, as Dr. Wyman tells us there is no calcification present. However, in the Massachusetts General Hospital cases,[4] reported in 1948, only half had calcification visible by x-ray examination — chiefly along the diaphragmatic surface, was it not? That leads me to the final consideration of what was done. Was it a decortication or just a decompression? I do not know.

It is possible that a Hodgkin node might have been in this picture, but I do not believe so. I am still going to make my first choice tuberculosis.

DR. CASTLEMAN: A needle was introduced below the xiphoid and driven posteriorly and superiorly into the pericardium; a large amount of thin amber-colored, slightly bloody fluid was present; about 280 cc. was withdrawn and replaced with about 180 cc. of air. That was the procedure that was done before the operation.

Dr. Harwood, would you tell us your thoughts about the patient before operation?

DR. HARWOOD: Dr. Chapman summed up the clinical situation very well. We had an acutely ill patient who was getting worse all the time. Dr. Conger Williams saw her with me. It was perfectly obvious that she had pericarditis with an effusion and cardiac tamponade. The onset was so abrupt that we thought that there must be some acute infection — probably not tuberculous pericarditis, which I had always thought was rather slow in onset. We believed that we had ruled out a bacterial pericarditis because both the blood culture and white-cell count were normal and the pericardial fluid failed to show any bacteria. It was Dr. Williams' thought that she might have virus pericarditis, and for that reason we gave her Chloromycetin. However, the Chloromycetin did not help. We believed we would lose the patient if we did not find out whether she had tuberculous pericarditis or not. It was with the idea of finding out that we agreed that a biopsy was justified.

CLINICAL DIAGNOSIS

Pericardial effusion, ?tuberculous.

DR. CHAPMAN'S DIAGNOSIS

Tuberculous pericarditis, with effusion.

ANATOMICAL DIAGNOSIS

Tuberculous pericarditis.

PATHOLOGICAL DISCUSSION

DR. LAMAR SOUTTER: The biopsy was simple to do, particularly after aspiration of fluid from the pericardium. The aspiration enabled us to estimate the thickness of the pericardium. Injection of air into the pericardium gave us a good outline of the heart. I wonder if Dr. Wyman would show the film that demonstrates this. The biopsy was performed through the fourth interspace anteriorly. This biopsy gave us an immediate diagnosis, with little hazard to the patient. By being able to establish the diagnosis, we could start treatment at once — a distinct advantage.

DR. CASTLEMAN: Could you say that the x-ray picture could not be due to metastatic carcinoma? Was that in the differential diagnosis?

DR. HARWOOD: We thought of that as a possibility but did not think the type of fever was consistent with it.

DR. WYMAN: I thought of that possibility but excluded it. In this film after air injection the margin of the pericardium on the inner aspect can be seen fairly well in several projections. There is a shaggy, irregular, frond-like appearance to the surface of the heart and to the pericardium itself. I do not see the characteristic nodules that I would expect to see if it were metastatic carcinoma.

DR. CASTLEMAN: The biopsy that Dr. Soutter took confirmed Dr. Chapman's diagnosis of tuberculosis, following which she apparently received a large amount of streptomycin.

DR. HARWOOD: Following the operation she had two interesting findings: She developed pleurisy on both sides, with pain, friction rub and a small amount of ascites. These were interpreted as being due to a hematogenous spread of tuberculosis, although we had no proof of it. She was started on streptomycin and improved only slightly at first, as I recall. She had para-aminosalicylic acid, which she could not tolerate. Dr. Theodore Badger, whom we asked to see her, suggested that she be given the sodium salt of para-aminosalicylic acid; this she was able to take in full dosage. Her fever subsided and she began to recover. She was in the hospital for six months; at the end of five months her sedimentation rate was normal, but then she developed rheumatoid arthritis, so we were no longer able to get any information from this test. She was continued on the para-aminosalicylic acid for about ten months and had streptomycin for about seven months; she has had two short courses of it since then, and she is now completely off therapy

of any kind, except for limited activity. She goes to work two or three hours, three or four times a week.

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CASE 38142

Presentation of Case

A forty-three-year-old woman was admitted to the hospital because of intermittent lower-quadrant pain.

Two months prior to entry she first noted the gradual onset of crampy lower-abdominal pain, which subsided spontaneously in one hour. She had no further trouble until one month before admission, when she again noted similar crampy lower-abdominal pain that was a little more severe on the right side. This also subsided spontaneously after a few hours. She was examined in the Out Patient Department three weeks before entry; no abnormal findings were noted on physical examination. A barium-enema examination made five days before entry was negative. The day following this she again began to have dull, steady lower-abdominal pain, more severe on the right side, that gradually increased in severity. The night before admission, following an enema, she became nauseated and vomited 5 to 6 times during the night and once on the morning of admission. The vomitus was greenish in color; no blood was noted. She remained nauseated until admission. She had for a long while been subject to occasional bouts of constipation requiring "salts" for relief, but in the near past she had had a normal bowel movement each day until the day before admission. For the 24 hours before admission there had been no bowel movement and no passage of gas. There was no recent weight loss or urinary symptoms.

She was gravida I, para I. Menstrual periods occurred every 28 to 30 days and lasted 4 to 5 days, with a moderate flow. There had been no recent change in this, except that during the last menstrual period, which began 31 days before admission and lasted 5 days, the flow had been somewhat heavier than usual. Twenty years prior to entry, x-ray films were taken because of infertility and she was told that she could have no more children because of a "blocked" tube. There had been no serious illnesses or operations in the past.

Physical examination revealed a somewhat obese woman in moderate distress. The heart and lungs were normal. The abdomen was distended, with spasm in the lower abdomen decreasing towards the costal margin. There was cough and rebound tenderness referred to the right lower quadrant. There was generalized tenderness in the lower abdomen, greatest on the right. No enlarged organs or masses were felt. Normally pitched peristaltic sounds were heard. Pelvic examination showed a moderate amount of yellowish-white vaginal discharge. Movement of a normal cervix caused pain. There was tenderness in both vaults, much more marked on the right. No definite masses or tumors were noted; bimanual examination was unsatisfactory because of the abdominal spasm. On rectal examination there was marked tenderness on the right.

The temperature was 101.6°F., the pulse 120 and the respirations 26. The blood pressure was 130 systolic, 80 diastolic.

Urine obtained by catheter had a specific gravity of 1.023; the sediment contained 5 white cells and 2 red cells per high-power field. Examination of the blood showed a hemoglobin of 12 gm. and a white-cell count of 10,400. The nonprotein nitrogen was 21 mg. per 100 cc. and the sodium 132.1 milliequiv. and the carbon dioxide 28.7 milliequiv. per liter. Vaginal smears were negative for tumor cells, gram-negative intracellular diplococci and diphtheroids. Barium-enema examination showed a completely filled colon, with reflux into a normal-appearing terminal ileum. No obstruction or filling defect was noted.

A Miller–Abbott tube was passed and the patient was started on antibiotics. For the first few hours after admission she was reasonably comfortable. Then she began to complain of severe crampy pain, maximal in the right lower quadrant, and intermittently vomited bile-stained clear fluid. The abdomen became rigid and no peristalsis was heard on auscultation. The white-cell count was 11,600. A plain film of the abdomen showed a small amount of gas in the small intestine and a greater amount in the large bowel. There was a suggestion of a defect at the tip of the cecum, raising the question of a mass extrinsic to the cecum, in the right lower quadrant. She improved somewhat on supportive therapy but continued to be febrile. On the third hospital day a plum-sized tender mass could be felt high in the midline on rectal examination.

On the fourteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Charles G. Mixter, Jr.*: The protocol, as presented, gives a somewhat confusing picture of the patient's course and disease, and I suspect that there are probably many "red herrings" in it. The history suggests disease in the right lower abdomen for the most part, but on the other hand the symp-

*Assistant in surgery, Massachusetts General Hospital.

toms at one time were noted to be bilateral, and at the end of the protocol I come across the sudden appearance of a plum-sized mass in the midline on rectal examination. The history as given is perfectly consistent with disease in and about the terminal ileum, the cecum, the appendix, the uterus or adnexa and possibly even the lower urinary tract on the right side.

If I am to explain all the symptoms given in the protocol with one diagnosis, I must postulate a disease that first, and in a somewhat chronic fashion, gave symptoms two months prior to entry, with increasingly severe symptoms appearing just before the date of entry and becoming markedly accentuated during her short hospital stay.

I believe I can, with justification, rapidly rule out the urinary tract as a source of the complaints, inasmuch as the pain was not consistent with the usual types of urinary difficulties, such as a ureteral stone or an ascending pyelonephritis; furthermore, the urine examination revealed 5 white cells and 2 red cells per high-power field. One would certainly expect more if there were urinary-tract disease, and I believe I can possibly explain these findings on the basis of inflammation, external, but in proximity, to the urinary tract.

Two items in the protocol in particular draw attention to the genital tract; these are the evidence of a blocked tube in the past and the slightly changed menstrual period twenty-one days before admission. Furthermore, on pelvic examination, motion of the cervix caused pain and there was tenderness in both vaults, more marked on the right. Also, it is conceivable that the plum-sized mass described might possibly have been connected with the uterus or adnexa. The history and symptoms do not suggest neoplastic disease, although this must always be considered in a patient of this age; they suggest more strongly the possibility of a low-grade inflammation or infection, possibly an ischemia. Certainly it would be unusual for any neoplasm in the genital tract to give such symptoms unless as a result of necrotic breakdown or as a result, say, of a twisted ovarian neoplasm. Several conditions immediately come to mind; the first possibility, in view of the previous history of a blocked tube, is a pyosalpinx, possibly with rupture, and the formation of a pelvic abscess. The abscence of gram-negative intracellular diplococci or diphtheroids would certainly not rule this out. It is, however, surprising that this could not have been distinguished by pelvic examination, but a definite statement is made that pelvic bimanual examination was unsatisfactory because of the abdominal spasm. Such a process might well have accounted for some disorder in the menstrual pattern, particularly at the time of her last one, if the process was becoming more acute, as it apparently was. Such a process as this could easily have accounted for the findings on physical examination and the temperature of 101.6° and elevated pulse and respirations, together with a moderate amount of ileus. I believe such conditions as a tubal pregnancy or endometriosis can probably be ruled out. One would expect a tubal pregnancy to go on to a more fulminating course, and there is little to suggest a pregnancy at this particular time. In view of the rather long history it is, of course, possible that an endometrioma or large chocolate cyst can rupture with the production of intraperitoneal signs, but one would not expect them to be of this severity. One other possibility is that of a twisted ovarian tumor, which might well account for the previous slight attacks of abdominal discomfort, together with the palpation of a tender mass on rectal examination and an elevated white-cell count and elevated temperature. However, one would expect to find the symptoms more localized to one portion of the abdomen than was the case in this patient.

Among the diseases that one certainly must discuss and consider is appendicitis. Certainly there is nothing in the history as given that is against this diagnosis, although it is far from a classical description. One could easily postulate the development of acute appendicitis with localized perforation and abscess formation, with the resulting partial ileus and the gradual progression of this condition to the point where generalized ileus and eventually a pelvic abscess became established. Furthermore, by x-ray examination there is a suggestion of a defect at the tip of the cecum, suggestive of a mass extrinsic to the cecum in the right lower quadrant. I see no way in which I can exclude this diagnosis.

May I see the x-ray films?

Dr. Stanley M. Wyman: There was only one barium-enema examination; that was made five days before entry in the Out Patient Department. It shows a normal-appearing colon and a short segment of grossly normal-appearing terminal ileum. The colon emptied well, and the mucosa, as far as I can see, is not remarkable. The films taken on admission during the acute episode show a tube coiled in the stomach. A small amount of barium remains in the colon from the barium enema. There is the pattern of more than the usual amount of gas in the small bowel but no frank distention at this time. Although there is a question of a soft-tissue fullness in the right lower abdomen, it is not sufficiently clearly defined to permit me to say it is a frank lesion. The film of the lower chest and upper abdomen shows no free gas that I can see.

Dr. Mixter: I have taken it for granted that the patient could not have had an acute mechanical obstruction of either large or small bowel, in view of the type of vomiting, the lack of mention of any high-pitched or abnormal peristalsis and the lack of any x-ray evidence of such a condition. It

is my impression, however, that she did have a partial ileus, probably going on to almost complete ileus, in view of the distention, vomiting and eventual loss of peristalsis. For this reason I shall rule out mechanical causes of obstruction, either extrinsic or intrinsic to the bowel, unless such lesions might have gone on to perforation and the development of peritonitis. A possible explanation of the patient's complaints might be regional enteritis that had progressed to the point of abscess formation. To support this one can look back to the history of previous attacks of lower-abdominal pain and the change in bowel habits from constipation to regularity in the near past. Patients with this disease do not always, but as a rule do, give a past history more suggestive of a diseased bowel, with weight loss, cramps and a mucoid type of diarrhea. The x-ray films do not help me, for no good examination was made of the small bowel, and the reflux into the terminal ileum may not have been sufficiently high to have outlined such a process. Tuberculosis of the small bowel might also give the same type of picture. As far as the large bowel is concerned, I believe this can be ruled out by means of the essentially negative barium-enema examination.

A number of other conditions might be considered, but I believe that on the evidence at hand they may be rapidly discarded. Among these one might mention perforation of the bowel by a foreign body, Meckel's diverticulum, possibly with gangrene, typhoid, a psoas abscess, a pyometrium and an internal hernia of the Richter type.

In summary, I believe that the history and physical signs as given indicate an intraperitoneal inflammatory process, probably localized in the right lower quadrant, which progressed to a pelvic type of peritonitis. This impression is substantiated by the history of lower-abdominal pain on the right side, increasing in severity, accompanied by signs of intraperitoneal irritation such as spasm, tenderness and cough and rebound tenderness, and eventually producing ileus, as evidenced by the distention, vomiting, obstipation and decreasing peristalsis. The suggestion of a mass extrinsic to the cecum in the right lower quadrant may have been further evidence of the presence of such a process. Statistically, I believe that appendicitis with perforation would be the most likely diagnosis. However, inasmuch as this is rarely a statistical exercise and because of the evidence discussed above, I shall hazard a guess that the primary diagnosis was pyosalpinx with perforation.

Clinical Diagnosis

Appendiceal abscess.

Dr. Mixter's Diagnosis

Pyosalpinx, with perforation.

Anatomical Diagnosis

Ruptured pyosalpinx.

Pathological Discussion

Dr. Benjamin Castleman: The surgeon made an incision directly over the point of maximum tenderness in the right lower quadrant. The exact nature of the disease was not immediately apparent. There were a great many adhesions, and the bowel was stuck together in such a manner that exploration had to be carried out in a cautious manner. Finally, rather deep in the pelvis, a collection of pus was entered that was estimated to be between 200 and 500 cc. After further exploration a huge retort-shaped pyosalpinx, which apparently had ruptured, produced an abscess in the pelvis and then sealed itself off, was removed. When we received the specimen, the ovary was embedded near the distal end, so she really had a salpingo-oöphoritis. The patient did very well postoperatively and when seen five months later had no complaints.

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CROSS PURPOSES

EVEN when the unpredictable individuals who comprise mankind can be credited with the best of intentions—as is many times the case—they nevertheless seem to find themselves often at cross purposes. Oneness of mind and unanimity of intent are lacking, particularly in a democracy, in which it is considered not good taste to liquidate the opposition. Where the opposition is disposed of by any means other than persuasion, democracy does not exist.

In matters of health the same sturdy independence of mind exists. It is common observation that many apparently legitimate extensions of health service meet at first with opposition, sometimes from unexpected quarters. Often progress along lines of public health, actually a respectable and on the whole a peaceful pursuit, is taken to be in conflict with private practice, despite the more intelligent conclusion that the two are directed, from every reasonable point of view, toward the same ultimate goal.

Sometimes apparently small differences in opinion will create amazing degrees of controversy where it might have been expected that hardly any room for disagreement should exist at all. And so often the mere sitting down together of opposing factions around the board reveals reasons for the opposition as well as for the original proposal and reveals also that misunderstandings may have developed on both sides that require a co-operative effort for their resolution.

In Massachusetts the simple proposition that there should be improved oversight of the health of school children, as provided by law, has given rise to controversy over the status of the school physician and the definition of his duties, and of the private physician and his privileges, as well as of the rights of parents and of the children themselves in the matter.

The attempts of the Department of Public Health to outline the details of reasonable standards in this oversight (as provided by law), aided by a committee of the Massachusetts Medical Society, raised certain quite unexpected controversial points — unexpected partly because the program had been approved by the Council of the Society. The important change that has been desired for several years by pediatricians and pediatric organizations concerned the acceptance of a policy of periodic, reasonably thorough appraisal of school children at intervals of three or four years, instead of the annual passing-in-review that has been the immemorial custom. The acceptance of this principle and the principle that the family physician should first have his opportunity for fulfilling the requirements of the appraisal was the important consideration; the actual opposition was based on certain details of operation that were easily modified when the minds were persuaded to meet in an atmosphere of harmony.

In all the successive attempts that are made to extend the benefits of health protection to all the people, the physician whose livelihood depends on

LIBRARY APR 15 1952 MANHATTAN KANSAS

the private practice of medicine must be assured that he, too, will be protected. He must not, however, expect to be protected at the expense of the health of the community. With the extension of health services the independently practicing physician acts too often as if he were at bay, even when the only intention is that of drawing him into a cooperative undertaking openly designed for better service to the community.

The highest possible degree of security for all will be attained by a consistent attitude of reasonableness. In the case of the physicians of the Commonwealth, both reason and their tradition of public service, based on humanity, will undoubtedly lead them to accept this progressive step, even as the Council of their Society has accepted it. As William Lloyd Garrison once said: "With reasonable men I will reason; with humane men I will plead."

THE VAGINAL SMEAR

TEN years ago, in his original communication, Papanicolaou suggested that the vaginal smear might be used to screen large numbers of women for the early detection of uterine cancer. In 1945 the Director of the Division of Cancer and Other Chronic Diseases of the Massachusetts Department of Public Health decided to inaugurate an experimental study to determine, from an administrative point of view, the diagnostic value of the cytologic method. His final report, which appears in this issue of the *Journal*, indicates, because of both the expense involved and the relatively few cases discovered on screening, that it is not feasible for a state health department to offer this test on an extensive scale for women without gynecologic symptoms. On the basis of the reported study, this conclusion seems amply justified.

Screening by the cytologic method has been employed in a number of clinics for large groups of symptomless women and for smaller groups by private physicians in their offices. The detection of unsuspected uterine cancer has varied from about 3 per thousand in the larger series to about 10 per thousand in the smaller groups. In an unpublished series of 700 women coming to an internist's office, 10 positive smears uncovered 7 unsuspected and 2 clinically suspected carcinomas of the cervix, an incidence of unsuspected cases of 1 per cent. Lombard's findings of 3 unsuspected cases in 1654 women examined and his conclusion that "the incidence of uterine cancer among individuals without gynecologic symptoms proved to be less than one per cent" is consistent with other studies and is neither unexpected nor disappointing.

The accuracy of cytologic diagnosis is dependent on the interest of the person taking the specimen, the experience and intellectual quality of those making the microscopical diagnosis and the type of case studied. It is well known that the method is least accurate in cases of advanced cervical cancer and in the presence of vaginal bleeding. Moreover, these two groups are least in need of screening — the one because the lesion is clinically evident, the other because biopsy or curettage is indicated in all women with abnormal bleeding. Had the Advisory Committee been more experienced in this type of screening (an impossibility six years ago), women with abnormal bleeding and those with advanced cancer would have been excluded from the study, and repeat smears would have been requested on all cases reported "questionable." Thus a larger proportion of symptomless women would have been included (the group in which the method is most useful), and examination of a second smear would, in most cases, have made it possible to arrive at a definite positive or negative diagnosis. Had these steps been taken, a more favorable report as to the diagnostic value of the vaginal smear might have resulted.

Large-scale screening for uterine cancer may be at this time impracticable, not only because of the low yield and the consequent cost per case detected but also because the special qualifications necessary for accurate interpretation of cells are not commonly found. It may be some time before an adequate number of technicians and pathologists trained in cytologic diagnosis will be available. Until then, screening will have to be confined to those clinics and private physicians who have at their disposal reliable cytologic laboratory assistance.

Dr. Lombard and his group deserve great credit for their early evaluation of a new laboratory method. From their report it is evident that large-

scale screening at the state level is now neither feasible nor financially justifiable. It must be kept in mind that the method is capable of greater accuracy than it was possible to demonstrate in Dr. Lombard's report.

MEDICAL BOOKPLATES

A SMALL but enthusiastic band of physicians collect, as a hobby, the bookplates or book labels of doctors. These collectors have been active in various countries for more than fifty years. In England the field was extensively cultivated by the late George C. Peachey, a distinguished medical historian at the turn of the century. The cult was taken up by Walter Hamilton, another Englishman, who wrote on French bookplates, especially on the rare sixteenth-century plates of Rabelais. In France, Henri André not only designed bookplates for physicians but wrote a book, *Les Ex-Libris de Médecins et de Pharmaciens* (1908). In America, George T. Palmer[1] was inspired by a fellow collector, Roland G. Curtin,[2] and Morris Fishbein[3] built up a collection in Chicago, now in the Army Medical Library in Washington. One of the largest accumulations was made by Edwin S. Potter of Philadelphia, who later moved to Santa Barbara and had his little known book, "Serpents in Symbolism, Art and Medicine," privately printed in 1937. His theme was constructed largely around his bookplates.

Other collectors of recent years are MacDowel Cosgrave in Ireland, Vaclav Rytir in Czechoslovakia, Kuno Waehmer[4] in Germany, M. Rodriguez Codola in Spain, A. D. Henriksen and Kay P. Nielsen[5] in Denmark, Ines Luomanen in Finland and Marie C. Croockewit[6] in Holland. Waehmer lists all the known bookplates of German physicians up to the year 1870. Henriksen and Nielsen reproduced 50 Danish medical *ex libris* and Marie Croockewit, a thorough and meticulous scholar, lists 662 Dutch medical bookplates. These enthusiasts add an international flavor to the bookplate game; they are known to the sophisticated as "ex librists." Medical librarians are also prone to join the cult; good collections are to be found in Des Moines, Iowa; Lawrence, Kansas; New Orleans, Louisiana; Worcester, Massachusetts; and Toronto, Canada — aside from those in the larger libraries at Washington, Philadelphia, London and Amsterdam.

Among the better known bookplates of physicians in America are those of John Bernard Sweet of Newburyport, dated about 1795, Oliver Wendell Holmes, John Shaw Billings, Edwin S. Potter and Harvey Cushing. Some, like Arpad Gerster and Alfred Jerome Brown, have designed their own *ex libris*.

So extensive has become the literature on medical bookplates that a bibliography of the subject is most welcome. This has recently been issued by Samuel X. Radbill, a well known Philadelphia collector, in a nicely printed book by the Anthoensen Press of Portland, Maine.[7] Some famous medical bookplates are reproduced, and an introductory essay traces the historical development of bookplates of medical interest.

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EDUCATION À LA MODE

THE seventh annual Postgraduate Lecture Course of the Massachusetts Medical Society and the Massachusetts Department of Public Health, which began on March 3, has reached its midway mark. For the benefit of those who may have missed the previous notices and wish to avail themselves of the opportunities for easy erudition presented by the remaining weeks of the course, the program for the next fortnight is reprinted on another page of this issue of the *Journal*, and the rest will follow in succeeding weeks.

Never, presumably, in the history of medical postgraduate education have so many been able to benefit so much from the efforts of so many, for the faculty of what was once designated only half in jest as Sanders University consists of more than 80 experts in the various fields of medicine. Here, indeed, is the true *Cafeteria Hippocratica*, where he who reads may grab a tray and run!

Mrs. Eliza M. Willis, M.D., delivered a valedictory address at the Syracuse (so-called) Medical College.

Boston M. & S. J., *April 7, 1852*

MASSACHUSETTS MEDICAL SOCIETY

POSTGRADUATE LECTURE COURSE

John Ware Hall
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Monday, April 7. DISORDERS OF ELECTROLYTE METABOLISM. Chairmen: Drs. Arnold S. Relman and William B. Schwartz.

7:00–7:20 p.m. **Effects of Electrolyte Disorders on the Electrocardiogram.** Dr. John P. Merrill.

7:30–7:50 p.m. **Electrolyte Metabolism in Gastrointestinal Disorders.** Dr. William Wallace.

8:00–9:00 p.m. **Round-Table Discussion of Postoperative Electrolyte Disorders.** Drs. John Raker, Alexander Leaf, Arnold S. Relman and William B. Schwartz.

Wednesday, April 9. *4:00–6:00 p.m.* PANEL DISCUSSION ON FRACTURES ABOUT THE ELBOW JOINT IN CHILDREN. Chairmen: Drs. Russell F. Sullivan and Carter R. Rowe. Discussers: Drs. Russell F. Sullivan, Carter R. Rowe, George W. Van Gorder, Alexander P. Aitken, [David F. Grice, E. Everett O'Neil and Paul I. O'Brien.

Monday, April 14. *7:00–9:00 p.m.* PANEL DISCUSSION ON PERIPHERAL VASCULAR DISEASES. Chairmen: Drs. Edward A. Edwards and Joseph R. Stanton. Discussers: Drs. Robert Linton, Theodore C. Pratt, Robert Wilkins, Edward A. Edwards and Joseph R. Stanton.

Wednesday, April 16. CHEST DISEASES. Chairmen: Drs. Carlton R. Souders and Richard H. Overholt.

4:00–4:30 p.m. **Practical Methods for the Evaluation of Pulmonary Function.** Dr. Edward A. Gaensler.

4:30–5:00 p.m. **The Significance of Hemoptysis.** Dr. Carlton R. Souders.

5:00–5:30 p.m. **Hidden Bronchiectasis in the Asthmatic Patient.** Dr. James H. Walker.

5:30–6:00 p.m. **The Value of the Boston Chest X-Ray Survey.** Dr. John H. Cauley.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Biological Actions of the Adenine Nucleotides. By H. N. Green, M.A., M.D., M.Sc., professor of pathology, University of Sheffield, and H. B. Stoner, M.D., research assistant, Department of Pathology, University of Sheffield. 8°, cloth, 217 pp., with 64 illustrations and 37 tables. London: H. K. Lewis and Company, Limited, 1950. 25s. net.

This special monograph discusses in detail the action of the nucleotides in shock and other pathologic conditions. The various chapters discuss the chemistry, metabolism and the general biologic action of adenosine triphosphate, the effect of purine derivatives on the cardiovascular and respiratory systems, the influence of magnesium and calcium on nucleotide activity, adenosine shock and the possible role of the nucleotides in pathologic states. The various chapters are documented with lists of references, there is a good index and the publishing is excellent. This valuable monograph should be in all medical libraries.

The Changing Years: What to do about the menopause. By Madeline Gray, M.S. 8°, cloth, 224 pp. Garden City, New York: Doubleday and Company, Incorporated, 1951. $2.75.

Mrs. Gray is a professional writer, who, stimulated by her own needs, devoted four years of research to the problems of the menopause.

NOTICES

PHI DELTA EPSILON FRATERNITY (BETA LAMBDA CHAPTER)

The annual lecture of the University of Vermont Chapter of Phi Delta Epsilon will be given on April 10 at 8:15 p.m. at the Fleming Museum Auditorium in Burlington, Vermont. Dr. William Dameshek will speak on "Hemolytic Anemias." All interested persons are invited to attend.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association announces the following programs in its Evening Lecture Series:

April 22 — "Operation for Coronary-Artery Disease," by Dr. Claude S. Beck, professor of cardiovascular surgery, Western Reserve University School of Medicine. Discussers: Drs. Dwight E. Harken, Monroe J. Schlesinger and Samuel A. Levine.

April 25 — "A New Method of Treating Recurrent Intestinal Obstruction," by Dr. Victor P. Satinsky, Director of Surgical Research, Albert Einstein Medical Center (Southern Division), Philadelphia. Discussers: Drs. Sara M. Jordan and Robert E. Gross.

April 29 — "The Problem of Calcification of Bone," by Dr. Alexander B. Gutman, professor of medicine, Columbia University College of Physicians and Surgeons. Discussers: Drs. Joseph C. Aub and Walter Bauer.

These programs are held at 7:00 p.m. in the New Cheever Amphitheatre of the Dowling Building of Boston City Hospital.

All interested persons are invited to attend.

AMERICAN NEUROLOGICAL ASSOCIATION

The seventy-seventh annual meeting of the American Neurological Association will be held at the Hotel Claridge, Atlantic City, New Jersey, May 8-10.

VENEREAL-DISEASE SEMINAR

A venereal-disease seminar, sponsored by the Public Health Service in conjunction with state health departments of the New England and Middle Atlantic states, will be held May 21 and 22 at the Hotel Bradford, Boston. Medical and health workers from 10 states will discuss their common problems; the seminar will be divided into one day of clinical discussion and one day devoted to public-health technics of controlling venereal disease. Physicians, nurses, social workers and other interested persons are invited to attend.

CONFERENCE ON AGING

The University of Michigan Fifth Annual Conference on Aging will be held in Ann Arbor, Michigan, July 24-26, 1952.

Prospective registrants may apply to Dr. Wilma Donahue, Institute for Human Adjustment, Room 1510, Rackham Building, Ann Arbor.

BOSTON UNIVERSITY SCHOOL OF MEDICINE ALUMNI ASSOCIATION

The Boston University School of Medicine Alumni Association will hold its seventy-second anniversary meeting on May 3 at the School of Medicine Auditorium, 80 East Concord Street, Boston, 2-4 p.m. A symposium on Cardiovascular Surgery will be presented.

PROGRAM

Management of Cardiac Trauma — Dr. Joseph P. Lynch, instructor in surgery, Boston University School of Medicine; visiting surgeon for thoracic surgery, Massachusetts Memorial Hospitals, Boston City Hospital and St. Elizabeth's Hospital.

Constrictive Pericarditis — Dr. John W. Strieder, professor of clinical surgery, Boston University School of Medicine; surgeon-in-chief for thoracic surgery, Boston City Hospital and Newton-Wellesley Hospital; visiting surgeon, Massachusetts Memorial Hospitals.

Surgery of the Mitral Valve — Dr. Dwight E. Harken, assistant clinical professor of surgery, Harvard Medical School; visiting surgeon for thoracic surgery, Boston City Hospital; surgeon, Peter Bent Brigham Hospital.

Treatment of Coarctation of the Aorta — Dr. Robert E. Gross, Ladd Professor of Children's Surgery, Harvard Medical School; surgeon-in-chief, Children's Medical Center.

The association's annual meeting and banquet will be held in the Dorothy Quincy Suite of John Hancock Hall at 6 p.m.

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The Spring Clinical Assembly of the Massachusetts Academy of General Practice will be held at Springfield on April 23.

A morning clinical session will be presented at Springfield Hospital under the direction of Dr. William Kaufmann.

PROGRAM

"Metabolism of Iron and the Management of Its Deficiency" — Dr. Howard P. Kennedy.

"Unexpected Dividends from Chest X-Rays" — Dr. W. Fenn Hoyt.

"Intramedullary Fixation of Fractures" — Dr. Elmer E. Franseen.

"The Management of Bronchial Asthma" — Dr. H. Bernard Tillman.

"Degenerative Changes in Diabetes Mellitus" — Dr. Jacob I. Weisman.

"Spinal Anesthesia in Obstetrics" — Dr. Harry L. Strachan.

"Psychosomatic Medicine: A Demonstration of the Therapeutic Interview" — Dr. Calvert Stein.

A luncheon and afternoon session will be held at the Hotel Kimball.

Dr. Stuart Cosgriff, of the Presbyterian Hospital, New York City, will discuss "The Use of Anticoagulants." Dr. Malvin White, of Boston, will speak on "The Role of Plastic Surgery in the Treatment of Common Disorders in General Practice." The after-dinner speaker will be Dr. Jerome L. Leon, of the Riverside Hospital, New York City, who will discuss "Narcotics and the Adolescent."

SOCIETY MEETINGS AND CONFERENCES

APRIL 2–30. Springfield Hospital. Page 433, issue of March 13.

APRIL 3–5. Frank E. Bunts Educational Institute. Page 434, issue of March 13.

APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

APRIL 5 AND MAY 3. New England Society of Anesthesiologists Postgraduate Education Course. Page 996, issue of December 20, and page 476, issue of March 20.

APRIL 7–9. American College of Allergists. Page 390, issue of March 6.

APRIL 7–16. Postgraduate Lecture Course. Page 559.

APRIL 7 AND 21. Boston Floating Hospital. Page 521, issue of March 27.

APRIL 8. New England Society of Anesthesiologists. Page 522, issue of March 27.

APRIL 10. Phi Delta Epsilon Fraternity (Beta Lambda Chapter). Page 559.

APRIL 10. Mistakes in Diagnosis of Angina Pectoris and Coronary Occlusion. Dr. Howard B. Sprague. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

APRIL 10–15. Boston City Hospital House Officers' Association. Page 476, issue of March 20.

APRIL 14–25. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

APRIL 16. Phi Chi Medical Fraternity — Delta Chapter (Tufts). Page 521, issue of March 27.

APRIL 17–19. Boston Lying-in Hospital and Children's Hospital. Postgraduate Course in Obstetrics and Pediatrics. Page 433, issue of March 13.

APRIL 21–25. American College of Physicians. Page 522, issue of March 27.

APRIL 21–25. Cancer Seminar. Page 114, issue of January 17.

APRIL 22, 25 AND 29. Boston City Hospital House Officers' Association. Page 559.

APRIL 23. Massachusetts Academy of General Practice. Springfield. Notice above.

APRIL 23. New England Obstetrical and Gynecological Society (Spring Meeting). Hartford, Connecticut.

APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

APRIL 25 AND 26. Texas Medical Center. Page 354, issue of February 28.

APRIL 26. Boston City Hospital Alumni Association. Page 476, issue of March 20.

APRIL 26. Alumni Association of Long Island College of Medicine. Page 434, issue of March 13.

MAY 3. Boston University School of Medicine Alumni Association. Notice above.

MAY 3. Annual Meeting. Massachusetts Association of Medical Technologists, Inc. Page 433, issue of March 13.

MAY 8–10. American Neurological Association. Page 559.

MAY 10. Boston Dispensary Proctologic Session. Page 433, issue of March 13.

MAY 10 AND 11. American Electroencephalographic Society. Page 390, issue of March 6.

MAY 11–17. Pan-American Convention of Gastroenterology. Page 434, issue of March 13.

MAY 19–22. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 19–23. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

MAY 21 AND 22. Venereal Disease Seminar. Page 559.

MAY 22–24. American Academy of Pediatrics. Page 522, issue of March 27.

MAY 26–28. Minnesota State Medical Association. Annual Meeting. Page 316, issue of February 21.

MAY 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.

MAY 29–31. American Academy of Dental Medicine. Page 476, issue of March 20.

JUNE 5–8. American College of Chest Physicians. Page 280, issue of February 14.

JUNE 18–20. Massachusetts Public Health Conference. Amherst.

JUNE 19–21. American Association of Genito-Urinary Surgeons. Page 434, issue of March 13.

JUNE 22–26. American Society of Medical Technologists. Twentieth Annual Convention. Portland, Oregon.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–11. International Congress of Dietetics. Page 434, issue of March 13.

JULY 7–12. International Diabetes Federation. Page 316, issue of February 21.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

JULY 24–26. Conference on Aging. Page 559.

AUGUST 25–29. American Congress of Physical Medicine. Page 476, issue of March 20.

AUGUST 31–SEPTEMBER 6. Interamerican Congress of Cardiology. Page 522, issue of March 27.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies. Mount Washington Hotel, Bretton Woods, New Hampshire.

OCTOBER 28–30. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

NOVEMBER 3–7 AND 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

JULY, 1953. International Congress on Medical Librarianship. Page 316, issue of February 21.

(Notices concluded on page xiii)